

ARCHIVES OF DISEASE IN CHILDHOOD

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Annotations

69 Editorial

70 Proper use of growth hormone R D G Milner

72 Somatic gene therapy for genetic disease C Kinnon, R J Levinsky

Original articles

74 Effect of artificial food colours on childhood behaviour I Pollock, J O Warner

78 Association between risk factors for coronary heart disease in schoolboys and adult mortality rates in the same localities W Freeman, D C Weir, J E Whitehead, et al

84 Growth and feeding problems after repair of oesophageal atresia J W L Puntis, D G Ruson, C E Holden, et al

89 Urinary growth hormone excretion as a screening test for growth hormone deficiency J M Walker, P J Wood, S Williamson, et al

93 Absence of effect of dipyridamole on renal and platelet function in diabetes mellitus D M Gibb, D Dunger, M Levin, et al

99 Clinical monitoring of steatorrhoea in cystic fibrosis M P Walters, J Kelleher, J Gilbert, et al

103 Optic nerve hypoplasia: associations and management J Roberts-Harry, S H Green, H E Willshaw

107 Carbohydrate deficient serum transferrin in a new systemic hereditary syndrome H Stabler, J Jaeken

112 Fenfluramine in Prader-Willi syndrome: a double blind, placebo controlled trial M Selikowitz, J Sunman, A Pendergast, et al

115 Growth in haemophilic boys after HIV infection K J Pasi, M A Collins, A K Ewer, et al

119 Sleep habits and height at ages 5 to 11 M C Gulliford, C E Price, R J Rona, et al

123 Tracheostomy N J Freezer, S W Beasley, C F Robertson

127 Supraventricular tachycardia in infants: response to initial treatment N Sreeram, C W...

130 Myopathy with hypophosphatasia S S Seshia, G Derbyshire, J C Haworth, et al

132 Colitis caused by food allergy in infants S M Hill, P J Milla

134 Chronic intussusception A C Page, J E Price, J R Salisbury, et al

135 White noise and sleep induction J A D Spence, D J Brown, A Le...

137 Platelet antigens in varicella associated thrombocytopenia

139 Is... diabetes

Controversy—
reviews of a book

Current topic

Review

Personal practice



P24,942

ARCHIVES OF DISEASE IN CHILDHOOD

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ARCHIVES OF DISEASE IN CHILDHOOD

Editorial

The shape and design of the journal have changed this month. About 60 years ago, when the journal was first published, paper was manufactured in sheets and the standard size of a page was called crown quarto. We continued to use this size despite the introduction of paper produced and printed as a continuous roll, and the adoption of the A4 format as the standard size by our younger sister paediatric journals. We have changed the shape of the journal because it provides several advantages to the author and reader. The larger page has five vertical grids and allows the printing of tables and illustrations of different sizes more flexibly. There is now a greater chance of tables appearing on the same or facing page as the relevant text. More original data are being published and we hope to avoid the wide tables that are printed vertically and irritate the reader. The larger cover will provide the space for the increasing numbers of titles.

The *Archives of Disease in Childhood* was the first of the specialist journals published by the British Medical Association and each journal has developed a layout that has depended on the foibles of the editorial committee. This personal flavour is attractive to the reader, but provides difficulties for the keyboard operator at the printers who may have to set articles from several different journals within a day. Technical editors may change posts and the initiation of a new incumbent may be traumatic. The new design of the journal has been adopted by all the other specialist journals in the publishing house, and we hope that this uniformity will be as successful as the introduction of the Vancouver style for references.

In contrast with the abrupt change in the appearance of the journal, changes in philosophy have been introduced slowly. Our editorial committee has met yearly to audit the quality of published material and to provide fresh ideas. Each year we publish more pages and this has enabled us to publish a similar proportion of the submitted articles and

also provide a substantial number of review articles, which allow specialists to become aware of developments in other fields. The increased number of pages has allowed us to accept papers of high quality and originality that may appeal to only a small proportion of our readers. We no longer expect that every article will be read, or understood, by all our subscribers. The introduction of associate editors and the statistical assessment of all papers before acceptance has helped us to select papers in the specialised areas. One of the suggestions of the editorial board which we implemented in 1989 was a deletion of the subheading 'short reports' on the cover. It was pointed out that the short reports were original articles and that this subheading was superfluous and denigrating. We are still willing to publish papers in the short report format but single case reports must contain novel material.

Although peer review has been the basis for decisions on medical publications for many years, the review process has not received detailed assessment. The first international congress on peer review was held in May in Chicago prompted by *A Difficult Balance*.¹ There were papers on publication bias and how to avoid it, the opinions of authors about referees' reports, and the prevention of fraud. There were suggestions that readers should be told which parts of a journal were not peer reviewed, for example book reviews, letters, and some review articles. In one journal 25% of advisors were willing to sign their reports for the benefit of the author, but there was disagreement as to whether signed reports were as helpful to the editor. As authors we appreciate the anguish produced by a rejection letter and as no other selection aid has been suggested we will continue to make changes in our procedures to improve the quality of peer review.

¹ Lock S. *A difficult balance*. London: Nuffield Provincial Hospitals Trust, 1985.

Annotations

Proper use of growth hormone

Growth hormone treatment is in a state of flux. While it is gratifying that a product which was recently in such short supply should now be available in unlimited quantity thanks to advances in biotechnology, the achievement has been a costly one and the pharmaceutical industry naturally wishes to recoup its investment and make a profit. Only one company in the United Kingdom currently holds a product licence for somatropin (authentic recombinant growth hormone) but competition is expected daily. At a round price of £5000 per patient year there is keen interest by the industry, the profession, and the government as well as the patients and their parents in who should get growth hormone. The equally important questions of who should prescribe, dispense, and pay for growth hormone are interlocked with clinical decision taking but must remain at the fringe of this annotation.

Who needs growth hormone?

The ready availability of somatropin has been followed by an explosion of research into its clinical use. For example somatropin is known to be equipotent with the previously extracted pituitary hormone, free from viral contamination, and daily administration gives a better height velocity than treatment three times a week.¹ But the main thrust and excitement in clinical research has come from the discovery of categories of patients who grow faster when given growth hormone but who are not classically growth hormone deficient. Today, it is possible to create three diagnostic categories: (i) growth hormone *deficient*, where there is unequivocal growth hormone deficit both clinically and biochemically, (ii) growth hormone *responsive*, where growth hormone has been proved to increase height velocity long term in children who are not classically growth hormone deficient, and (iii) an *experimental* category where preliminary results of treatment suggest that growth hormone may be beneficial, but confirmation is awaited.

GROWTH HORMONE DEFICIENT PATIENTS

The clearest examples involve damage or destruction of the hypothalamo-pituitary axis as seen in craniopharyngioma, cerebral irradiation, or in developmental anomalies such as septo-optic dysplasia. The diagnoses of 'isolated growth hormone deficiency' or 'panhypopituitarism' are slightly less satisfying because clearly something is wrong with the axis that is not detectable by current imaging techniques. The vital common denominator is that in all cases of growth hormone deficiency the patient is short, growing slowly, and has an absent or unequivocally subnormal plasma growth hormone response to pharmacological or physiological testing.

GROWTH HORMONE RESPONSIVE PATIENTS

Both the amplitude and frequency of growth hormone pulses increase with age in childhood and at any given age a large child secretes more growth hormone than a small one.² There emerges the concept of a continuum of growth

hormone secretion: between normal growth hormone secretion stimulating normal growth and the unequivocally growth hormone deficient patient there lies a grey zone in which the child secretes some growth hormone but not enough to optimise growth potential. The cause of subnormal growth hormone secretion lies at a hypothalamic level or above and may be organic or functional. Studies with growth hormone releasing hormone quickly led to the discovery that up to half the patients identified as 'isolated growth hormone deficiency' had hypothalamic rather than pituitary pathology.³ Psychosocial deprivation causes slowing of growth and may mimic growth hormone deficiency, both of which remit on correction of the deprivation.⁴ The concept of 'growth hormone insufficiency' may be easy to grasp,⁵ but the clinician in consultation still faces a diagnostic dilemma.

When patients with subnormal growth hormone secretion were first characterised a decade ago the term 'normal variant short stature, NVSS' was used. Subsequently they have been called 'constitutional growth delay, CGD' or 'short slowly growing children, SSGC', but no matter what name is used the patient is defined as one who is short, growing slowly, and who responds to growth hormone treatment despite having normal growth hormone biochemistry.⁶ Clearly the scope for missed diagnosis and misguided clinical practice is immense. Paediatricians must be vigilant in their search for pathology, be it organic or functional, and wary of advocating drug treatment for children who are symptomless and predicted to achieve a socially acceptable adult height. Patients diagnosed as 'normal variant short stature' merit a clinical trial of growth hormone treatment but this must be offered in a setting where professional auxology is available to document height velocity off and on growth hormone. If treatment is undertaken an increase of height velocity of more than 2 cm/year over six months is justification for continuing.

Turner's syndrome is a clearer example of growth hormone responsiveness. There is evidence that growth hormone secretion in Turner's syndrome may be subnormal in later childhood because of lack of enhancement of pituitary sensitivity to hypothalamic stimulation by ovarian steroids.⁷ Growth hormone improves linear growth rate in patients with Turner's syndrome: both chromosomally classic patients and in mosaics, as shown by national trials from six countries. In the large multicentre trial from the United States, 50-70% of patients with Turner's syndrome who received growth hormone with or without steroids for four years achieved or exceeded their predicted adult height.⁸ Clinical experience in the United Kingdom,⁹ confirmed elsewhere, shows that not every patient with this syndrome will respond to growth hormone, but this problem can be overcome with the aid of professional auxology by using each girl as her own therapeutic bioassay. My view is that growth hormone treatment should be discussed with all patients and their families.

EXPERIMENTAL GROWTH HORMONE TREATMENT

The abundance of growth hormone has encouraged

clinicians to evaluate its potential benefit in other conditions. Growth hormone secretion and treatment was evaluated in two groups of children with intrauterine growth retardation who did not show catch up growth in the first year.^{10 11} In both studies a minority of the subjects had abnormal patterns of physiological growth hormone secretion, but most responded with a clinically important increase in height velocity over one year. Similar results were obtained irrespective of whether the subjects had stigmata of Silver-Russell syndrome. In the larger study two dosage regimens (15 or 30 U/m²/week) were used and the children grew faster on the higher dose.¹¹ Unfortunately increased height velocity was associated with accelerated bone maturation leading to the conclusion that an improved final height could not be expected from the treatment.

The idea of growth hormone treatment in uraemia is initially surprising because uraemic children have high concentrations of growth hormone in their plasma, but two clinical trials have reported impressive increases in height velocity over six to nine months in response to somatrem (recombinant methionine-growth hormone) or somatropin in conventional doses.^{12 13} This is potentially very important and further detailed information is awaited on the longer term response in height, tissue composition, and osseous maturation.

The potential expense of growth hormone treatment should not inhibit clinical scientists from exploring new uses for the hormone, but it lays a heavy burden on them to design good experiments. Those analysing the results of such work must be satisfied that improved growth is achieved in absolute terms and not only in biostatistical units such as standard deviation scores. Clinical practice should advance cautiously; only in adulthood will the full consequences of paediatric treatment be appreciated.

Dose?

The dose of growth hormone used in the United Kingdom has arisen from historical practice; most patients are on 12 or 14 U/week given as 2 U subcutaneous daily injections, or less commonly as three injections of 4 U/week. This results in a wide range of dosage in terms of body weight or surface area and some paediatricians have been pragmatic and halved the dose for patients under 20 kg. Improvements in the packaging of growth hormone now mean that this rough and ready approach is no longer appropriate. The doctor needs to calculate what dose will optimise therapeutic effect at minimum cost. This is likely to be calculated on a body weight basis and given daily.

A review of growth hormone dose response showed clearly that growth rate is directly proportional to the logarithmic dose given¹⁴; in other words a physiological effect merges into a pharmacological one. While it is easy to agree that physiological growth hormone replacement is desirable, the profession is divided on the use of growth hormone as a pharmacological tool. Some investigators take the view that if a given dose does not produce the effect they are seeking in a novel group of patients such as those described as 'normal variant short stature' then more will be better.¹⁵ They monitor their clinical trials empirically by looking for side effects such as glucose intolerance, but I find this approach conceptually unsatisfactory. If growth hormone works in physiological replacement dosage there is *a priori* evidence that the body lacked growth hormone; if pharmacological dosage is required to produce an effect there is no endogenous growth hormone lack and growth hormone treatment is not indicated.

Comment

This annotation has focused on the use of growth hormone

to stimulate growth in children and other therapeutic possibilities that may have considerable impact on paediatric practice, such as growth hormone induction of anabolism postoperatively,¹⁶ have of necessity been excluded.

Cost/benefit considerations come into every consultation where growth hormone treatment is discussed with a family. Happily, good rapport has developed in the United Kingdom between family practitioners and hospital based paediatric endocrinologists whereby the former prescribe and oversee the administration of this costly product and the latter provide a diagnostic and monitoring service that is essential for the correct use of the hormone.

The potential risks associated with growth hormone treatment must always be discussed before treatment is recommended. Physicians can now give unequivocal reassurance that there is no risk of Creutzfeldt-Jakob disease when hormone made by recombinant biotechnology is used. The question of leukaemia is more complex and a recent comprehensive review concludes: 'Though no clear evidence of a strikingly augmented leukaemia incidence is found world-wide, the available data call for increased attention'.¹⁷ Other risks such as diabetes are negligible so long as growth hormone is used in physiological replacement dosage. This can be defined as the amount required for normal growth in a growth hormone deficient subject. Growth hormone induced gigantism illustrates dramatically how the hormone can stimulate growth pathologically and I would not consider it good clinical practice to use high dose growth hormone regimens in refractory patients whatever their primary diagnosis.

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Somatic gene therapy for genetic disease

Recent advances in recombinant DNA technology have led to an increase in our understanding of the molecular basis of many genetic diseases. Approximately 3500 different human genetic diseases are known, and as the genes responsible for these diseases are identified and cloned, many advances in treatment and maintenance will be made. These advances have already translated into improved methods for the prenatal diagnosis of many diseases and the use of recombinant gene products in treatment regimes. It is envisaged, however, that with further developments it will soon be possible to correct the genetic defects themselves in affected individuals, through the use of somatic gene therapy techniques. The potential for this form of treatment has generated much interest and the possible applications of somatic gene therapy have been much discussed.¹⁻⁴ For the purposes of this annotation, however, we are confining the discussion to those genetic diseases which are currently treated by bone marrow transplantation.

Somatic gene therapy is defined as the correction of a defective or absent gene with its cloned functional equivalent. It differs from germline gene therapy in that the gene is only introduced into the somatic cells of the patient and not into the germline (that is, sperm or ova). Therefore, the gene can only be expressed in those cells into which it was introduced and their progeny cells, but it cannot be passed on to subsequent generations of children.

Most cases of genetic disease are the result of a point mutation rather than a gene deletion, and this means that the defective gene is still present, though not necessarily active, in the affected cells. Therefore, the introduction of a functional gene in addition to the defective gene would result in gene augmentation. However, because of the non-specific nature of the integration event where the gene is inserted randomly into the human genome, a variety of problems may arise. These could include non-expression of the introduced gene or insertional mutagenesis, whereby a normally active gene is silenced or a silent deleterious gene may become activated. Despite these potential problems, this model has been the most widely studied so far and currently offers the best prospect for the treatment of genetic diseases.

A much more difficult technique would be true gene replacement whereby the defective gene is removed from the affected cells and replaced with a functional gene in the correct orientation and chromosomal location. Such gene replacement would be technically difficult, although a model for gene targeting involving homologous recombination is being developed in the mouse⁵; this is currently only applicable to germline gene therapy.

Methods of gene insertion

A variety of methods for the introduction of cloned genes into cells have been suggested and these can be classed into two groups: physical and viral. The physical methods include coprecipitation with calcium phosphate and the use of polycations or lipids to complex with DNA, cell fusion techniques using liposomes, erythrocyte ghosts and protoplasts, microinjection, and electroporation techniques. While large numbers of cells can be treated at once (except by microinjection) these techniques have the disadvantage that the efficiency of integration is low and multiple copies of the DNA are usually inserted.

The first viruses used in gene expression experiments

were the DNA tumour viruses (SV40, polyoma) and the adenoviruses. Recently the work has focused on murine retroviral vectors, particularly those based on Moloney murine leukaemia virus.

Retroviruses have a number of useful features that makes them suitable for use as vectors for gene therapy. In contrast with the physical methods of introducing DNA into cells, retroviral vectors can infect up to 100% of target cells and the DNA is usually integrated as a single copy. Once integrated into the host genome the provirus acts as a cellular gene in that it is faithfully passed onto progeny cells. The production of progeny virus is non-lytic, leading to the establishment of permanent, viral producing cell lines which give high titre virus for infection.⁶ The proteins required for viral encapsidation (the *gag*, *pol* and *env* genes) can be supplied *in trans*, which means that replication defective retroviruses can be produced that are capable of only one round of infection, which removes the problem of constant reinfection of cells. The possibility exists, however, that infective viruses could be produced subsequent to gene insertion if they recombine with endogenous retroviruses. Furthermore, retroviral vectors can only encode up to seven kilobases of introduced DNA, which in most cases is not sufficient to encode a full length gene and its appropriate control sequences. Loss of control sequences may lead to inappropriate tissue expression and low levels of expression of the gene product.

In the future it is possible that more efficient, higher titre viral vectors capable of encoding larger pieces of DNA may be developed based on vaccinia, adenoassociated, herpes, bovine papilloma, and other viruses.

Criteria for somatic gene therapy

There are a large number of genetic diseases that could potentially be treated by somatic gene therapy. The candidate disorders for this type of treatment must meet the following criteria: (i) the disorder must have a severe and predictable phenotype, (ii) the defective gene must have been identified and cloned, (iii) expression of the gene product should not require precise regulation, nor particularly high levels of expression to correct the defect, and (iv) there must be a suitable delivery system for the implantation of the genetically modified cells.

Currently, the most suitable disorders for this type of treatment are diseases that affect the hematopoietic system. The main reason for this is that there already exists a suitable method for the reintroduction of the treated cells through bone marrow transplantation. Indeed, diseases such as severe combined immunodeficiency due to adenosine deaminase deficiency may be successfully treated by allogeneic bone marrow transplantation.⁷ The gene for adenosine deaminase has been cloned and a considerable amount of effort has already been put into developing strategies for the treatment of this disease by somatic cell gene therapy,² although enzyme replacement treatment with polyethylene glycol stabilised adenosine deaminase presents another possibility.⁸ Other candidate disorders of this type currently include purine nucleoside phosphorylase deficiency, chronic granulomatous disease, Gaucher's disease, and the haemoglobinopathies such as the thalassemias and sickle cell disease.

The idea of introducing genes into bone marrow stem cells is particularly attractive as these cells should

permanently correct the genetic defect. Indeed, studies in mice have shown that genes can be stably introduced into bone marrow stem cells by retroviruses and expression in differentiated progeny cells has been detected for some time afterwards.⁹⁻¹¹ Although stem cells have been identified with some certainty in mice,¹²⁻¹³ there is still some way to go in defining their human equivalents.¹⁴⁻¹⁵ There also remains the problem of putting the human stem cells into cycle, as proviral integration is dependent on DNA replication and at present there is no efficient means of achieving this. Another problem is the question of gene regulation. In order to get tissue specific gene expression at the appropriate level it is necessary for the gene to be under the control of appropriate regulatory elements and in the vast majority of cases, with few notable exceptions,¹⁶⁻¹⁷ these elements have yet to be defined.

Ethical considerations

Apart from the technical problems of ensuring tissue specificity and adequate levels of gene expression there remain a number of medical and ethical issues. First, for diseases in which the gene product is produced by bone marrow derived cells, in some cases, it may be necessary to create space within the bone marrow compartment in order to decrease competition between infected and uninfected cells thereby providing a selective advantage for the stem cells carrying the functional gene. The currently used chemotherapy or radiotherapy techniques for bone marrow ablation may be sufficient but eventually monoclonal antibodies targeted at the relevant cells in the bone marrow may provide a less toxic alternative. Complete marrow ablation may not be necessary as it has been shown in the partially ablated thalassaemic mouse model that the introduction of only 5% of normal bone marrow cells may correct the defect.¹⁸

It will probably be necessary to define the nature of the defect in individual cases as in the small number of families where a gene deletion rather than a point mutation exists the product of the introduced gene may prove to be immunogenic, thereby rendering the treatment ineffective. The techniques currently being developed allow the potential for insertional oncogenesis, as they all rely on random integration events. The only foreseeable way to overcome this problem is by gene targeting but this remains only a theoretical possibility at present.

In view of these problems, somatic gene therapy should, at present, only be considered for diseases that are fatal in early infancy or that carry a very poor prognosis with the currently available treatments. There needs to be an ethical debate in the United Kingdom to discuss issues well before the first attempt at treatment are contemplated. In the United States the machinery to obtain ethical approval is already in place whereby permission needs to be obtained from national bodies. No such national body exists in the

United Kingdom and there is the potential risk that such treatments will be carried out under the approval only of individual hospital ethical committees, the performance of which may vary widely. The European Medical Research Councils made a joint statement over a year ago to the effect that a national body in each country should consider all proposals for human gene therapy and ensure the application of agreed national guidelines. They recommended that early trials should be monitored by a central body.¹⁹ As most of the diseases that are currently being contemplated as suitable for such treatment affect the paediatric age group it may be appropriate for the British Paediatric Association to take part in the formulation of suitable ethical policies and in the formation of such a national body to assess and monitor the trials.

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ORIGINAL ARTICLES

Effect of artificial food colours on childhood behaviour

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Abstract

We performed an objective evaluation of 39 children whose behaviour was observed by their parents to improve on an artificial food additive free diet and to deteriorate with dietary lapses. Only 19 children completed a double blind placebo controlled challenge study with artificial food colours. In these children food colours were shown to have an adverse effect on a daily Conners' rating of behaviour, but most parents could not detect these changes. A pharmacological mechanism of food additive intolerance is proposed to explain these effects.

Ingestion of a number of artificial food additives has been shown to provoke urticaria¹ and asthma² in some individuals. The role of food additives in affecting children's behaviour is more controversial. Recent studies have been contradictory: one claimed that foods and food additives could provoke hyperactive behaviour in a group of very disturbed children with an unusually high incidence of atopy,³ while another failed to show any such association.⁴ These conflicting results are partly explained by methodological variations in trial design such as the use of placebos, the number of double blind challenges, and challenge doses.⁵ Most trials only employed a single cross over design^{3 4 6-10} when it has been argued that repeated cross over challenges are necessary to diagnose food intolerance.¹¹ One trial acknowledged a significant order effect that was difficult to explain.³ We have been involved in a study of the prevalence and mechanism of 'organic' food additive intolerance,¹² and took the opportunity to investigate children whose parents believed that their behaviour was adversely affected by artificial food additives.

Patients and methods

SUBJECTS

Thirty nine children between the ages of 2.8 and 15.3 years (mean 8.9) were recruited from a paediatric allergy clinic and from a population survey of food additive intolerance.¹² Inclusion in the trial was based on the parents' observations that various behavioural problems had improved on a diet that eliminated food additives. The diet of these children excluded food additives to a variable extent, although all excluded artificial food colours. According to the parents, deliberate or inadvertent consumption of food additives, even in small amounts,

precipitated the recurrence of their child's behavioural problems. The age of onset of these perceived food additive problems varied from less than 1 year to 9 years (mean 2.1) (table 1).

Parents stated that their children exhibited a variety of behavioural problems, which developed within several minutes, but occasionally up to 12 hours after consuming food additives. Poor concentration and excess fidgeting were identified as associated problems by most parents.

Most children attended normal schools, had no known neurological disorders, and had not received any psychiatric assessment. One child with idiopathic global retardation attended a school for the educationally subnormal, and one other child who had been diagnosed as being hyperkinetic and who had previously received methylphenidate was subsequently placed in a special school.

Children were included in the trial only if they were able to consistently swallow the size '0' capsules that contained the challenge material.

The parents were interviewed by IP using a standard questionnaire. The children underwent a general examination during which evidence of allergic disease was carefully sought. Skin prick tests to common allergens (cat, house dust mite, grass pollen, egg, milk) were performed to determine atopic state, and were considered positive if weals were greater than 3 mm after 10 minutes in the presence of positive histamine and negative saline controls.

STUDY PROTOCOL

For the duration of the trial, the food additive elimination diet of each child was maintained.

The trial consisted of double blind placebo controlled challenges with artificial food colours. The food colours chosen (tartrazine (E102) 50 mg, sunset yellow (E110) 25 mg, carmoisine (E122) 25 mg, and amaranth (E123)

Table 1 Clinical features (n=39)

Mean (range) age (years)	8.9 (2.8-15.3)
Sex (m:f)	29:10
No recruited from:	
Clinic	26
Population survey	13
No (%) with atopy	16 (41)
No (%) with atopic disease*	15 (38)
No (%) with other additive problems†	10 (26)
Mean (range) age of onset of additive intolerance (years)	2.1 (0-9)
Mean (range) reaction time after ingestion (hours)	2.5 (0-12)

*Asthma, eczema, or hay fever.

†Urticaria, gut upset, or headache.

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25 mg) are those most often implicated in adverse reactions to food additives.^{1 13}

Food colours were effectively disguised in gelatin capsules, which had been rendered opaque with iron oxide and could not be distinguished from placebo. One capsule was swallowed with breakfast throughout the seven weeks of the trial. The dose of additives in the 'active' capsules was chosen so as greatly to exceed the estimated daily intake.¹⁴ The placebo capsules contained lactose. During the seven weeks of the trial, 'active' capsules were taken daily throughout two separate weeks while placebos were taken during the remaining five weeks. Subjects were allocated randomly to one of two sequences of active and placebo weeks (table 2). The two sequences were designed to allow three clear weeks of placebo between 'active' challenge weeks with the week after an 'active' week designated a 'washout' period, when only placebo capsules were taken. Parents were informed that the weekly capsule challenges contained either food additives or placebo.

One or both parents completed a daily questionnaire of the child's behavioural and somatic symptoms throughout the trial. Ten behavioural questions were from the Conners' hyperactivity index, which is a questionnaire that has been frequently used in studies of hyperactivity.^{3 15} Ten further questions were entered to assess somatic symptoms commonly associated with allergies (wheeze, urticaria, eczema, etc). Each of the above items was recorded on a 0-3 scale of severity ('not at all', 'just a little', 'quite a lot', 'a lot').

Space was provided for daily comments. An overall weekly behaviour assessment was requested from parents in which the behaviour during each week was simply recorded as 'improved', 'the same', or 'worse'.

Wilcoxon rank (paired and unpaired) tests were used where appropriate for statistical analysis.

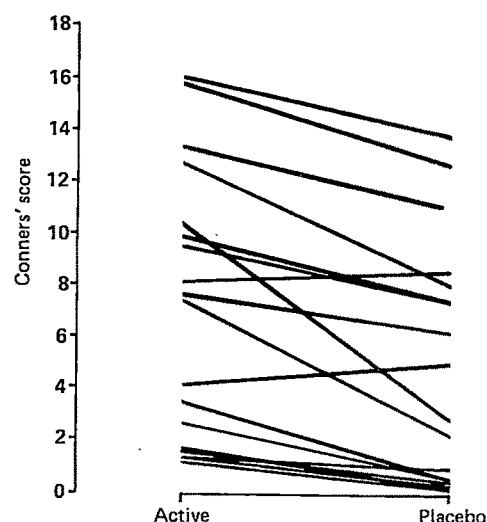
Results

Thirty nine children were entered into the trial, of whom only 19 completed the seven weeks. There was no significant difference between those who completed the trial and those who defaulted with regard to age, sex, and atopic state.

Five children were withdrawn from the trial without having taken any capsules: one child because the family emigrated and four because the parents, on further consideration, decided not to risk provoking behaviour problems. Five

Table 2 Study design showing the two randomly allocated challenge sequences

	Week 1	2	3	4	5	6	7
Sequence 1	A	W	P	P	A	W	P
Sequence 2	P	P	A	W	P	P	A
Week A (active): each capsule contained tartrazine (50 mg), sunset yellow (25 mg), amaranth (25 mg), and carmoisine (25 mg).							
Weeks P and W (placebo and washout): each capsule contained lactose.							



The mean daily Conners' behaviour score during the 14 active days and 21 or 28 placebo days. Higher scores (worse behaviour) are shown during active periods in all but two subjects. The scores are generally low. Differences between active and placebo are small but significant ($p < 0.01$ Wilcoxon rank sum test).

sets of results were either lost in the post or mislaid. Four children were withdrawn after parents noted unacceptable behavioural changes early in the trial. On breaking the code, two children (one of whom was globally retarded) were taking active capsules and the other two were taking placebos. Six children have not yet completed the trial and seemingly will not do so as they entered the trial up to 18 months ago. The results of the 19 children who completed the trial are therefore presented.

The mean daily behavioural scores during the two 'active' capsule weeks were significantly higher than on placebo ($p < 0.01$) (figure). The mean daily somatic symptom scores, however, did not differ between active and placebo ($p = 0.1$) (table 3). Changes in the behavioural scores were not associated with changes in the somatic symptom scores ($p > 0.5$) or with atopic state ($p > 0.1$). Those of the 19 who had claimed

Table 3 The mean daily Conners' behaviour score and somatic symptom score during active and placebo weeks ($n = 19$). The behaviour scores were worse during active weeks compared with placebo ($p < 0.01$). No significant difference was found in somatic symptom scores between active and placebo weeks ($p = 0.1$)

Case No	Mean daily behaviour score		Mean daily somatic symptom score	
	Active	Placebo	Active	Placebo
1	9.50	8.05	0.64	0.66
2	8.00	8.70	0.07	0.18
5	1.25	0.10	3.42	0.86
6	1.15	0.77	1.79	1.57
7	13.20	8.33	0.07	0
10	3.25	0.33	1.00	1.18
11	2.30	0.35	6.50	1.00
12	7.75	6.85	0.93	0.71
15	9.80	7.53	5.86	3.25
16	7.70	2.68	0.57	0
18	16.00	14.35	0.14	0.39
19	3.95	5.70	15.00	15.50
20	1.20	0.13	0	0.14
22	1.50	0	32.00	9.60
23	1.50	1.37	1.71	1.52
24	0.95	0.23	0.50	0.32
28	10.85	3.27	1.50	0.69
39	15.95	13.63	2.29	0.86
40	13.90	11.45	0.29	1.21

that additives provoked both somatic symptoms and affected behaviour were analysed separately and no significant effect of food colours on somatic symptoms was found ($p > 0.1$). In other words the changes in behaviour scores were not related to or secondary to changes in somatic scores.

There was no significant order effect between those who received active or placebo capsules first. Nor was there any difference between the scores of placebo or washout weeks, suggesting that there was little or no carry over effect from the active week into the next 'washout' week.

During the active weeks there was no difference between the behaviour scores on days 1 and 7 ($p \gg 0.25$). This finding suggests that the behavioural effect occurred early in the 'active' week giving no support to the suggestion that some food additive intolerance is the result of a cumulative effect of food additives.

A Conners' score of 15 or more has been employed in previous studies as a criterion of hyperactivity.^{3, 15} Only two children in the study had scores of 15 or more (that is, 15.95 and 16). The boy who had received methylphenidate after a diagnosis of the hyperkinetic syndrome completed the trial and had a mean daily behavioural score that was greater on placebo than 'active'.

Parents' overall weekly behavioural assessments (each week recorded as 'worse', 'same', 'improved') were analysed to see if they correctly identified the 'active' weeks as being 'worse'. The overall behaviour during each challenge week was compared by parents with behaviour while on an additive free diet. By excluding washout weeks, either five or six weeks remained for analysis (table 2). Two out of the 19 sets of parents did not complete any weekly assessments while one completed four out of five weeks. Table 4 shows 60/92 correct responses. Assuming that a response has a 50/50 probability of being right by chance alone, one would expect 46/92. The excess is 14 (SE 4.80), which is very significant. There is no evidence that some parents are better than others ($\chi^2_{16} = 20.95$, $p = 0.18$). If the results of each child are analysed individually after receiving two active and two or three placebo weekly challenges,

however, then all the weeks must be correctly identified by each parent to achieve significance.¹¹ Only two parents correctly identified all the challenge weeks (table 4).

Discussion

This study shows that a daily intake of 125 mg of a mixture of 'artificial' food colours can produce a measurable change in the behaviour scores of a group of children. This effect was unrelated to changes in somatic symptoms or to the atopic state of the children. Most parents were unable to detect the changes in behaviour at the end of each week. This disparity between the results of the behaviour scores and the parents' weekly assessments is important when it is remembered that entry into the study was based on the parents' claim to be able to detect when their children had consumed food additives. The results of the behaviour scores are not evident until somewhat time consuming calculations are performed. We believe this validates the objectivity of the challenge procedure and the methods used to monitor responses. The changes in the behavioural scores, although significant, were small (figure), and may not have been great enough for most parents to detect.

It has been claimed that it is almost impossible to disguise tartrazine challenges due to the additive's powerful colour.⁴ Opaque capsules, however, provided an effective and convenient blind challenge suitable for most food additives including tartrazine (an exception may be the sulphiting agents because they probably act by the inhalation of sulphur dioxide from a solution). It is possible that the capsules were being covertly opened by parents, although this seems very unlikely as their overall weekly behavioural assessments should then have been far more accurate than was the case.

The drop out rate is disappointingly high compared with many studies of allergic diseases but is probably more typical of psychiatric studies.¹⁶

All but two of the children in our study attended normal schools and had no major psychiatric or neurological diagnoses. Thus this study differs from any previous studies, which involved selected groups of children who sometimes had serious and unusual concurrent problems such as epilepsy.^{3, 6-10} As was noted in the results, only two children could be considered hyperactive on the basis of their Conners' behaviour score. As such, the results of this study are likely to be more clinically relevant to general paediatric and allergy practice. Moreover, these children were studied without any alteration in their daily routine, rather than being admitted and challenged in an artificial laboratory or ward setting. This may be an important factor as it is known that variables such as exercise can affect the development of an allergic reaction,¹⁷ and it is likely that other unknown variables exist.

The mechanism of food additive intolerance is uncertain. Over 3000 food additives of vastly differing chemical structure are in use, and it is unlikely that only one mechanism can account

Table 4 The parental weekly behavioural assessment. Each week is recorded as 'worse', 'the same', or 'improved'. Correct assessment of active week = 'worse', and placebo = 'the same' or 'improved'

Case No	Correct weekly assessments
1	5/6
2	2/5
5	4/5
7	3/5
10	6/6*
11	3/4
12	1/6
15	2/6
16	3/6
18	3/6
20	5/5*
22	4/5
23	4/5
24	5/6
28	3/5
39	4/6
40	3/5

*Only two parents correctly assessed all challenge weeks.

for all reported reactions. Egger *et al* suggested an atopic mechanism was involved in hyperactivity.³ Classical allergic reactions are unlikely to be involved, however, as there is minimal evidence of the involvement of specific antibodies,¹⁸ and furthermore, the presence of atopy did not correlate with behavioural changes in this study.

We suggest that a pharmacological mechanism of food additive intolerance is likely. Chemical mediators such as histamine and prostaglandins are involved in food additive induced urticaria,¹⁹ although one study failed to show any in vitro effect of tartrazine on the prostaglandin system.²⁰ Another study has shown that many food additives can cause histamine release from basophils.²¹ In this study, doses of food colours greater than the amounts that children are likely to consume produced changes in behavioural scores that were not detected by most parents.

Previous behavioural studies have generally shown no effect of smaller doses or only suggested an effect on children under 5 years of age.⁶⁻¹⁰ Therefore food additive intolerance may be mediated by the pharmacological release of histamine or other mediators. Behavioural effects may then result from subtle changes in pulse or skin temperature, etc, or by the action of other mediators capable of crossing the blood-brain barrier. Our own studies have shown that large doses (200 mg) of tartrazine produce small, albeit asymptomatic increases in plasma and urinary histamine in normal adults.²² Smaller doses of tartrazine in children, on a mg per kg basis, might be expected to have a similar effect.

Hyperactive behaviour has many causes.²³ It is probable that food additives given in very large doses may act as a pharmacological trigger in a small percentage of children with behaviour problems, although even in these children the effect may be small and clinically insignificant. We feel strongly that parents of children with behavioural problems should receive a sympathetic hearing and that their ideas are not dismissed out of hand. The many factors that are known to influence behaviour need to be explained to parents, as should the limited evidence for the role of food additives and foods in causing behaviour problems. It can also be useful to explain the possible transient nature of food additive intolerance.¹³ As dietary manipulation in children may result in nutritional inadequacy,²⁴ and may adversely affect health, it is important for a dietitian to assess children whose diets have been manipulated without professional guidance. Sometimes double blind challenges are of value clinically in showing

parents that food additives are not responsible for a particular symptom. Many desperate families are unaware of the benefit of child guidance, clinical and educational psychologists, family therapy, and other helping agencies, and doctors can assist by making the appropriate referral.

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Association between risk factors for coronary heart disease in schoolboys and adult mortality rates in the same localities

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Abstract

Risk factors for coronary heart disease were compared in fifth year boys (15-16 years old) from two schools that were chosen from localities with a fourfold difference in adult mortality from coronary heart disease. One school was in an underprivileged urban locality in the area of increased incidence of heart disease ('high risk') and the other in a semi-rural affluent locality with an incidence of heart disease similar to the national average ('low risk'). Smoking, hypertension, hypercholesterolaemia, obesity, physical fitness, and inactivity were evaluated as risk factors for coronary heart disease. Smoking, increased body fat, poor diet, and physical inactivity were found increased among pupils from the school in the high risk area compared with those in the low risk area. Lipids, maximum oxygen uptake, and hypertension were similar in both schools. The risk of coronary heart disease seems to reflect the adult mortality rates in the area. To reduce the overall incidence of coronary heart disease, health education should be directed towards prevention of smoking, improving diets, and increasing amounts of activity among school children, with special attention directed toward children in regions where there is a high mortality from coronary heart disease among adults.

There is strong evidence that although symptoms of coronary heart disease are first noticed in adult life, the disease starts to develop during childhood, and that prevention programmes starting in childhood could reduce the death rate from cardiovascular disease.^{1 2} In adults, epidemiological studies have identified several factors that increase the risk of coronary heart disease. Hypercholesterolaemia, cigarette smoking, and hypertension are the three main factors,³ but others include obesity,⁴ poor physical fitness,^{5 6} and physical inactivity.⁷ The extrapolation of risk factors to younger age groups is speculative, but it is recognised that their identification at an early age may indicate potential candidates for coronary heart disease in adulthood.⁸

In the borough of Solihull (West Midlands, United Kingdom), the 1983 standard mortality ratios (SMR) for ischaemic heart disease and acute myocardial infarction compared favourably with the national average (SMR 89 and 98, respectively).⁹ Mortality statistics for 1985 for people aged 50 and over within the borough of Solihull, however, identified an area with an

increased death rate from coronary heart disease (2.8/100/year), compared with that of the rest of the borough (0.7/100/year), which was similar to the national average. In order to evaluate whether the risk factors for coronary heart disease in children reflect this difference in adult mortality, we have investigated and compared the prevalence of primary and secondary risk factors in fifth year boys attending a school in the locality with an incidence of heart disease similar to the national average with boys from a school in the locality with an increased incidence of heart disease.

Methods

Two schools were selected for study, one in the locality where the incidence of heart disease was similar to the national average (low risk school) and one in the locality where there was an increased incidence of heart disease (high risk school). The fifth year boys in each school were divided into two groups for their physical education lessons, and one class was randomly selected for study. As the stratification of the pupils for physical education lessons was not made on sporting or academic abilities, but by the school timetable, it was considered that these pupils would be representative of their total populations. A total of 42/45 and 46/49 pupils from the low risk and high risk schools, respectively, were studied. The study was approved by the hospital ethics committee and both parents or guardians, and pupils, gave informed consent. The assessment of each pupil included a short medical questionnaire, a series of measurements to ascertain baseline values, an activity questionnaire, and an exercise test.

The medical questionnaire listed the current and past medical history of each pupil. Resting blood pressure was measured with a manual mercury sphygmomanometer (Accoson). Hypertension was defined as a systolic blood pressure greater than or equal to 136 mm Hg at the age of 15 years, and 142 mm Hg at the age of 16 years, and a diastolic blood pressure greater than or equal to 86 mm Hg at the age of 15 years, and 92 mm Hg at the age of 16 years.¹⁰ Pupils with a history of asthma were given a β_2 agonist from a metered dose inhaler before exercise to minimise exercise induced bronchoconstriction. Height and weight were measured. The body mass index was calculated from the ratio of weight/height² (kg/m^2); a body mass index of 27 kg/m^2 being taken as indicating obesity.¹¹ Skinfold measurements were made at four sites of the body (biceps, triceps, subscapular, and suprailiac) using Harpenden calipers

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(British Indicators Ltd), which allowed the calculation of the percentage of body fat.¹² We defined obesity as greater than 20% body fat.

An investigator filled in the questionnaire about participation in sports outside physical education lessons. The duration, frequency, and intensity (judged by the development of sweating or breathlessness) of each sporting activity was recorded. Each pupil was then placed in one of three activity level categories: category I—aerobic activities performed three times a week for 30 minutes and associated with sweating or breathlessness, or both (the minimum amount of exercise required to develop and maintain aerobic fitness¹³); category II—aerobic activities, either performed at least once a week for 30 minutes, or three times a week for 15–30 minutes, associated with sweating or breathlessness or both; and category III—pupils who were not doing sufficient activity to be placed in the above two categories. The questionnaire also listed how the children got to and from school, other after school activities, smoking history, and father's occupation. Smoking status was verified by measuring the exhaled carbon monoxide concentration (Morgan Ecocheck-EC50), and social class was assigned by father's occupation.¹⁴

The maximal multistage 20 metre shuttle running test (20-MST) was used to assess maximum oxygen uptake.¹⁵ Each pupil ran back and forth along a 20 metre track in a gymnasium at a speed prescribed by audio signals from a prerecorded tape in a cassette recorder. The running speed for the test started at 8.5 km/hour with increments of 0.5 km/hour each minute. Pupils received continuous encouragement, and were instructed to complete as many shuttles as possible. The test was stopped either by the investigator when the pupil could not keep up with the prescribed pace, or by the pupil when he was unable to continue. Maximum oxygen uptake was predicted using the final stage and the number of shuttles completed at this stage from tables for subjects under 18 years old.¹⁶ Performance on the 20-MST correlates well with the laboratory maximum oxygen uptake in boys of this age ($r=0.87$), and is therefore a valid test to estimate maximum oxygen uptake.¹⁷ As used by Wilmore *et al*, a maximum oxygen uptake of less than 45 ml/kg/min was regarded as a risk factor for coronary heart disease.¹⁸

Heart rate was measured at rest, at 15 second intervals throughout exercise, and for 10 minutes in recovery with a heart rate micro-computer (Sport Tester, Polar Electro). The maximum heart rate recorded at the end of exercise was compared with the predicted maximum heart rate for age ($220 - \text{age}$).¹⁹ The rate of recovery of heart rate for each pupil was assessed by calculating the time after exercise for the heart rate to return to half of the increase observed from rest to maximum.

On subsequent occasions, two 20 μ l samples of capillary blood taken from the thumb were analysed for cholesterol and triglyceride concentrations with a Reflotron analyser (Boehringer). The coefficient of variation has been documented by the manufacturers as 3% for both

cholesterol and triglyceride. A serum cholesterol of 5.2 mmol/l and serum triglyceride of 2.3 mmol/l were taken as the upper limits of normal.²⁰ To assess the dietary habits of each group an investigator filled in a questionnaire recording the food consumption of each pupil over the previous 24 hours. A dietitian coded each diet into good, average, or poor using criteria recommended by the National Advisory Committee of Nutrition Education.²¹

The unpaired Student's *t* test and the Wilcoxon rank sum test, when data were not normally distributed, were used to compare the discrete data between the pupils from each school. A one way analysis of variance was used when data were categorised by social class. All categorical data were analysed by the χ^2 test.

Results

Resting measurements were made and the questionnaire given to 42 of 45 (93%) and 46 of 49 (94%) of the fifth year boys from the low risk and high risk schools, respectively. Two of the three pupils from the low risk school who did not participate in the study had been refused parental consent, and one was absent for medical reasons. Three pupils from the high risk school were absent from school for the study period for non-medical reasons (Borstal and truancy).

Table 1 shows the physical characteristics and resting blood pressure of each group. The pupils in the high risk school were significantly shorter (95% confidence interval (CI): 0.01 to 5.9 cm) and had a higher percentage of body fat (95% CI: 0.4 to 4.0%) than the pupils in the low risk school. Two of 42 pupils in the low risk school (5%) and four of 46 pupils in the high risk school (9%) had more than 20% body fat, and by our definition were obese. The body mass index was not significantly different between schools. There were, however, three of 46 pupils from the high risk school (6.5%) with a body mass index greater than 27 kg/m², whereas no pupils from the low risk school had body mass indexes in the obese range. The pupils in the low risk school, however, had a significantly higher mean resting systolic blood pressure (95% CI: 0.5 to 11.5 mm Hg). In the low risk school the mean blood pressure was significantly raised in eight of 42 pupils (19%) with four pupils having a high systolic, and four pupils having a high diastolic, pressure. Five of 46 pupils (11%) from the high risk school were

Table 1 Physical characteristics and blood pressure measurements in fifth year boys in the low and high risk schools. Values are given as mean (SD)

	Boys at low risk school (n=42)	Boys at high risk school (n=46)
Age (years)	15.3 (0.5)	15.4 (0.5)
Height (m)	1.73 (0.1)*	1.70 (0.1)*
Weight (kg)	60.2 (7)	58.9 (13)
Body mass index (kg/m ²)	20.1 (2)	20.2 (4)
Body fat (%)	11.5 (4)	13.7 (5)*
Systolic blood pressure (mm Hg)	122 (11)	116 (14)*
Diastolic blood pressure (mm Hg)	73 (10)	70 (13)

* $p<0.05$.

Table 2 Smoking history of the fifth year boys in the low and high risk schools

	Boys at low risk school (n=42)	Boys at high risk school (n=46)
No (%) current smokers	7 (17)	13 (28)
No (%) who had given up smoking	4 (9)	11 (24)
No (%) who had never smoked	31 (74)	22 (48)*
No (%) pupils whose exhaled breath contained >64 ppm carbon monoxide	4 (10)	10 (22)
Smokers		
Mean (SD) No of cigarettes/week	51 (46)	60 (40)
Mean (SD) duration of smoking (years)	2.7 (1.8)	1.5 (0.9)

* $p < 0.05$.

hypertensive, with two pupils having a raised systolic blood pressure; two pupils having a raised diastolic blood pressure, and one pupil having both raised systolic and diastolic pressures.

Table 2 shows the smoking habits of the pupils. In the high risk school more pupils were current smokers or had given up, and significantly fewer pupils had never smoked. Of the professed non-smokers, no pupil had an exhaled carbon monoxide concentration above 6 ppm, thus verifying their smoking history.

The pupils degrees of activity showed that 16 of 42 (38%), and 14 of 46 (30%) pupils from the low and high risk schools, respectively, were doing effective aerobic exercise at least three times a week (category I). Twelve of 42 pupils from the low risk school (29%) and 11 of 46 pupils from the high risk school (24%) were

doing effective aerobic exercise at least once a week (category II). Fourteen of 42 pupils from the low risk school (33%) and 21 of 46 pupils from the high risk school (46%), however, were not performing effective aerobic exercise even once a week (category III). Of the pupils placed in category III, 12 of 14 from the low risk school (86%) but only 10 of 21 from the high risk school (48%) wished to increase their activity. Furthermore, more pupils from the high risk school watched three or more hours of television a night (low: 12 of 42 (29%) compared with high: 21 of 46 (46%)). In contrast, 41 of 46 pupils from the high risk school walked, ran or cycled to school (89%), compared with only 23 of 42 pupils from the low risk school (55%) ($p < 0.001$).

Thirty eight of 45 (84%) and 35 of 49 (71%) pupils from the low risk and high risk schools, respectively, consented to the shuttle running exercise test. There was no significant difference between the performance in the exercise test (mean (SD)) (low: 75 (20) compared with high: 71 (18) shuttles) and therefore in the estimated maximum oxygen uptake (low: 47.5 (5.6) compared with high: 46.5 (5.0) ml/kg/min) of the fifth year boys. There was a wide range in the maximum oxygen uptake in both schools, however, with 12 of 38 pupils from the low risk school (32%) and 11 of 35 pupils from the high risk school (31%) having a maximum oxygen uptake less than 45 ml/kg/min (fig 1). The average heart rates at rest, during exercise, and during recovery are shown in fig 2. The maximum heart rates of 200 (7) (range 186–215) beat/min for the low risk school and 200 (8) (range 184–219) beat/min for the high risk school, were similar. No pupil had a maximum heart rate of less than 90% of the predicted maximum, suggesting that each pupil gave maximum effort. In recovery, the time taken for the heart rate to fall to half of the increase observed from rest to maximum was not significantly different between the schools (low: 1.62 (0.55) compared with high: 1.48 (0.44) min).

Four boys from the low risk school and 11 boys from the high risk school had baseline measurements taken but did not perform the exercise test. At the low risk school, three of these four boys could not undergo the exercise test for medical reasons (uncontrolled asthma, leg injury, and shoulder injury). In the high risk school, however, only one of the 11 boys could not exercise on medical grounds (congenital heart defect); the remaining 10 did not wish to undergo the test. The 10 pupils from the high risk school who did not exercise for non-medical reasons had a significantly higher percent body fat (16.7 (6.0) %) than those exercising (13.0 (4.5)%) ($p < 0.05$), were more likely to be current smokers (five of 10 pupils, 50%) compared with eight of 35 (23%) pupils who performed the exercise test, and were more inactive with six of 10 (60%) pupils in activity category III, compared with 15 of 35 (43%) pupils who exercised.

Cholesterol and triglyceride concentrations and dietary histories were obtained for 37 of 45 (82%) and 29 of 49 (59%) pupils from the low and high risk schools, respectively. The concen-

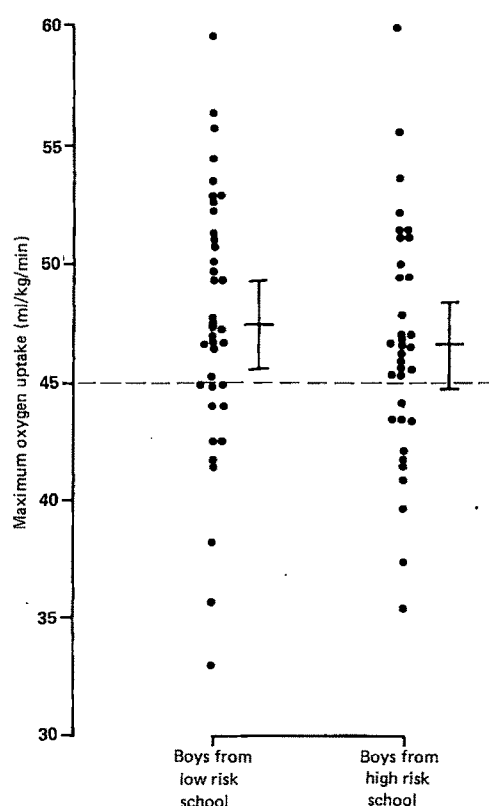


Figure 1 The maximum oxygen uptake for the fifth year boys from the low and high risk schools. Values are mean and 95% confidence intervals. The horizontal dashed line is the maximum oxygen uptake equivalent to 45 ml/kg/min.

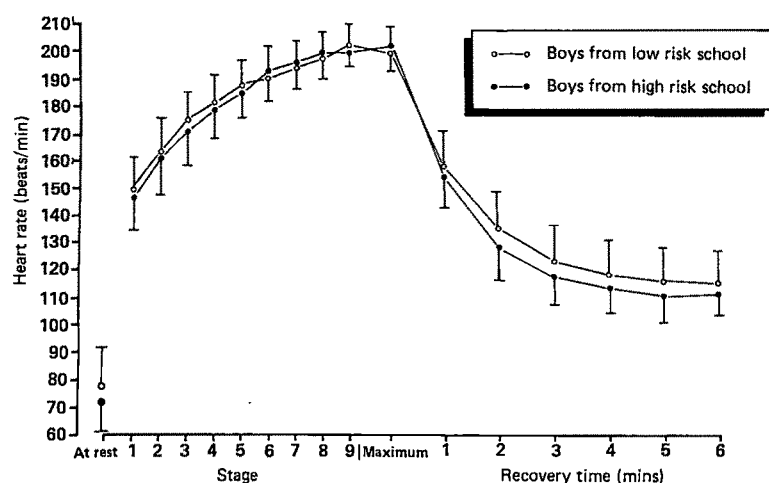


Figure 2 The mean (SD) heart rate at rest, during exercise, and during recovery for the fifth year boys from the low and high risk schools.

Table 3 Prevalence (%) of the risk factors for coronary heart disease in the fifth year boys in the low and high risk schools

	Boys at low risk school	Boys at high risk school
Primary risk factors		
Current smokers	7/42 (17)	13/46 (28)
Cholesterol concentration >5.2 mmol/l	0/37	1/29 (3)
Hypertension	8/42 (19)	5/46 (11)
Secondary risk factors		
Body fat >20%	2/42 (5)	4/46 (9)
Maximum oxygen uptake <45 ml/kg/min	12/38 (32)	11/35 (31)
Physical inactivity (category III)	14/42 (33)	21/46 (46)

Table 4 Social class distribution, based on the father's occupations, of the fifth year boys from the low and high risk schools. Figures are given as No (%)

Social class	Boys at low risk school (n=42)	Boys at high risk school (n=46)
I Professional	10 (24)	0
II Intermediate	14 (33)	4 (9)
IIIN (Non-manual/clerical)	4 (10)	0
IIIM (Manual/skilled)	11 (26)	21 (46)
IV Semi-skilled/manual	2 (5)	6 (13)
V Unskilled/manual	0	0
One parent (with mother)	0	6 (13)
Unemployed	0	7 (15)
Unable to code	1 (2)	2 (4)

Table 5 Social class differences in risk factors for coronary heart disease among fifth year pupils from both schools combined. Values are mean (SD) unless otherwise indicated

	1 Non-manual workers (classes I, II, IIIN)	2 Manual workers (classes IIIM, IV, V)	3 Unemployed or One parent families
Height (m)	1.73 (0.07)	1.71 (0.06)	1.70 (0.08)
Weight (kg)	60.5 (9.8)	59.4 (9.4)	59.4 (15.0)
Body fat (%)	11.8 (3.8)	13.2 (4.9)	13.6 (5.2)
Systolic blood pressure (mm Hg)	123 (10)	118 (14)	112 (13)
Diastolic blood pressure (mm Hg)	74 (10)	71 (11)	69 (16)
Cholesterol concentration (mmol/l)	3.94 (0.65)	3.91 (0.83)	4.30 (0.06)
Triglyceride concentration (mmol/l)	1.21 (0.37)	1.19 (0.44)	1.24 (0.47)
Maximum oxygen uptake (ml/kg/min)	48.3 (5.9)	47.1 (4.7)	44.4 (5.0)
Time for heart rate to return to half increase observed between rest and maximum	1.5 (0.6)	1.6 (0.4)	1.3 (0.3)
No (%) smokers	5/32 (16)	11/40 (28)	3/13 (23)
No (%) inactive (category III)	11/32 (34)	19/40 (48)	5/13 (39)

trations of cholesterol (low: 3.95 (0.66) compared with high: 4.07 (0.82) mmol/l) and triglyceride (low: 1.22 (0.45) compared with high: 1.19 (0.34) mmol/l) were not significantly different between the schools. One pupil from the low risk school had a triglyceride concentration above the recommended upper limit of 2.3 mmol/l and one pupil in the high risk school had a cholesterol concentration above the recommended upper limit of 5.2 mmol/l. Fewer pupils from the high risk school had either a good (low: seven of 37 (19%) compared with high: one of 29 (3%)) or average (low: 24 of 37 (65%) compared with high: 11 of 29 (38%), $p < 0.05$) diet. Indeed, the diets of 17 of 29 (59%) pupils from the high risk school were classified as poor, compared with only six of 37 (16%) pupils from the low risk school ($p < 0.001$).

Table 3 summarises the incidence of risk factors. The primary risk factor with the highest prevalence was smoking, with a higher percentage of smokers in the high risk school. The secondary risk factors of inactivity and a maximum oxygen uptake of <45 ml/kg/min were common in both schools, with a higher percentage of the pupils in the high risk school classified as physically inactive.

Not surprisingly there were large social class differences between the pupils from the schools as determined from their father's occupation (table 4). Pupils from both schools were placed into one of three social class categories; 1=non-manual workers (I, II, and IIIN); 2>manual workers (IIIM, IV, and V); and 3=others (unemployed, and pupils living with their mother). There were no significant differences in measurements analysed for social class, although there was a trend towards shorter stature, increased body fat, lower systolic blood pressure and lower maximum oxygen uptake in pupils with fathers in lower social classes (table 5). All pupils in social class category 3, however, were from the high risk school and all but four of the pupils from social class category 1 were from the low risk school. Therefore pupils from social class category 2 (manual workers-IIIM, IV, and V) in the two schools were compared. The pupils from the high risk school were shorter (low: 1.73 (0.05) compared with high: 1.71 (0.07) m), fatter (low: 11.8 (4.5) compared with high: 13.9 (5.0) % body fat), more inactive (low: 39% compared with high: 52% with activity category III), and there were

more smokers (low: 15% compared with high: 33%). These differences were not significant.

Discussion

We have documented the prevalence of primary and secondary risk factors for coronary heart disease in fifth year boys from two contrasting localities within a community that have a four-fold difference in mortality from coronary heart disease in adults aged 50 and over. The findings showed that there is an increased prevalence of a number of risk factors for coronary heart disease in schoolboys from the area with the higher adult death rate from coronary heart disease.

Smoking was the most prevalent of the primary risk factors in both schools, and there was a higher percentage of smokers in the high risk school. The high prevalence of smoking is relevant because the risk of coronary heart disease is proportional to the duration of smoking, and is highest in those who start before the age of 20 years.²² Furthermore a recent study has found that the protective high density lipoprotein cholesterol is reduced in children after taking up smoking,²³ and thus may be contributing to the development of another risk factor for coronary heart disease.

A cholesterol concentration above 5.2 mmol/l in adults carries an increased risk of coronary artery disease.²⁰ In our study, only one pupil (from the high risk school) had a blood cholesterol concentration above this, a finding that compares favourably with that in a group of 700 adolescents among which 9% had cholesterol concentrations above 5.2 mmol/l.²⁴ The measurement of total serum cholesterol may be too simplistic,²⁵ however, and estimation of high and low density lipoprotein subfractions of cholesterol might have shown differences among the pupils. Furthermore, the dietary survey showed that children from the high risk school had much poorer eating habits, which if continued into adult life would be expected to have an adverse effect on cholesterol concentrations.

The mean systolic blood pressure was higher in the low risk pupils, which does not reflect the differences in adult mortality from coronary heart disease within the community. The reasons for this are not clear. Nevertheless, five pupils (11%) from the high risk school and eight pupils (19%) from the low risk school were hypertensive, although this diagnosis was based on a single measurement of blood pressure, which may have been unreliable. The prevalence of hypertension in our study was, however, similar to that in a group of 14-18 year olds in which 17% were hypertensive.²⁶

The pupils from the high risk school were significantly shorter, which is not unexpected in view of the social class differences, but constitutes a further risk factor for coronary heart disease.²⁷ The boys from the high risk school also had a significantly higher mean percentage of body fat, which may be attributed to their different dietary habits. The prevalence of obesity, defined as greater than 20% body fat, was higher in the schoolboys from the high risk

school (9%) compared with the pupils from the low risk school (5%). Although the relevance of obesity as a secondary risk factor in heart disease for children is not well documented, studies suggest that 70% to 80% of obese children develop into obese adults, and therefore take this risk factor into adult life.²⁸

Poor physical fitness has been shown to be associated with an increased risk of coronary heart disease.^{5,6} The performance on the shuttle running test and the estimated maximum oxygen uptake of the fifth year boys were not significantly different between the two schools, and was slightly inferior to that of 23 Irish schoolboys aged 15-16 years, who achieved 82 shuttles.²⁹ About a third of the boys from both schools had a maximum oxygen uptake of less than 45 ml/kg/min, which is similar to the prevalence of this putative risk factor of 35% of the 308 boys aged 13-15 years quoted by Wilmore *et al.*¹⁸ The maximum oxygen uptake has got, however, a large inherited component. A further assessment of cardiovascular fitness was therefore made by measuring the recovery of heart rate after exercise, which also showed no significant difference between the pupils from the two schools. The results from the exercise test may, however, be biased by the higher number of boys in the high risk school who refused to take the exercise test. Baseline investigations showed that this group of boys were fatter, less active, and more were smokers.

Inactivity is associated with an increased risk of coronary heart disease.⁷ In this study, the amount of activity undertaken by each pupil was assessed by documenting each pupil's participation in sports, because daily activities are unlikely to raise the heart rate sufficiently to incur a training effect.³⁰ Almost half the pupils from the high risk school and a third of the pupils from the low risk school were classified as inactive, not performing vigorous exercise even once a week. Furthermore, pupils from the high risk school watched more television, were less willing to perform the exercise test, and were more reluctant to increase the amount of activity they undertook. This negative attitude towards exercise among the pupils from the school within the area of higher adult mortality from coronary heart disease suggests that lower degrees of activity may persist into adult life, possibly leading to reduced physical fitness.

The areas from which the schools were chosen show a large difference in their degree of underprivilege, as defined by Jarman,³¹ although Solihull as a whole was one of the most privileged family practitioner committee areas in the UK in 1985 (97th out of 98). This disparity between the two areas within Solihull was reflected by the higher unemployment, more one parent families, and lower social class of fathers of the pupils from the high risk school, which suggests that the schools were representative of their areas.

Social class is a strong predictor of coronary heart disease.³² Adults from the lower social classes have higher rates of smoking, more obesity, and are less physically active,³³ which reflects the differences in risk factors found in

our study of children. There was a trend, however, for an increase in risk factors for coronary heart disease in pupils from the same social class from the high risk school compared with the low risk school, perhaps suggesting a further environmental influence that was not accounted for by social class.

What are the interventional implications of these findings? Current studies in adults have shown little benefit of intervention on the mortality rates from coronary heart disease.³⁴ Behaviour and attitudes that lead to an increase in the risk of coronary heart disease seem to develop in childhood, and intervention in adults may well be too late to effect change. In order to reduce the overall incidence of adult coronary heart disease more effectively, it may be wise to concentrate on the reduction of risk factors among schoolchildren, paying special attention to those in regions of higher adult mortality. The prevention of smoking is of paramount importance in reducing the incidence of coronary heart disease. In addition, the higher prevalence of obesity and poor diet among the pupils from the school in the high risk area suggests that there is a place for dietary education for both children and parents. Exercise will not only improve physical fitness but can also favourably modify the cardiovascular risk profile by reducing cholesterol and blood pressure,³⁵ improving the high density: low density lipoprotein cholesterol ratios,³⁶ and preventing obesity.³⁷ The amounts of activity undertaken by the schoolchildren in our study are too low to obtain these benefits, and therefore they should be increased and then continued throughout life if protection from coronary heart disease is to be maintained.³⁸

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Growth and feeding problems after repair of oesophageal atresia

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Abstract

Of 230 families belonging to a support group for parents of children born with oesophageal atresia, 124 returned a detailed questionnaire on feeding history and growth. Being slow to feed, refusing meals, coughing or choking during eating, and vomiting at meal times were significantly more common than in 50 healthy control children. Anthropometric analysis indicated that almost one third of patients were growth retarded, although those with a primary oesophageal anastomosis were less likely to be stunted or wasted compared with children who had an oesophageal substitution preceded by an oesophagostomy. Feeding problems tended to resolve spontaneously but slowly, with half of all children still reporting some difficulties at 7 years of age. Parents were considerably worried by feed related symptoms and families benefited from mutual support. There is a need for additional help and advice to be provided both by hospital staff interested in nutrition and feeding disorders and those professionals involved with primary care.

Tracheo-oesophageal fistula with oesophageal atresia occurs in approximately one in 5000 births.¹ After surgery there is an overall survival rate approaching 90%,² and those who reach adulthood can expect to enjoy a normal life.³ Despite this, feeding difficulties in early childhood,⁴ and repeated respiratory problems,^{5,6} contribute to major disruption of family life.⁷ Although it seems that growth in patients reaching adulthood may well be normal,³ there is a lack of information concerning growth during childhood and the natural history of feeding problems. Feeding difficulties severe enough to affect nutritional state might be expected to influence prognosis in some children. The aims of this study were to determine the prevalence of certain feeding related symptoms in children who have undergone surgery for oesophageal atresia, to explore how parents coped, and to investigate any possible impact on growth.

Patients and methods

A detailed questionnaire relating to feeding behaviour was sent to all 230 families belonging to the Tracheo-Oesophageal Fistula Support Group (TOFS); an organisation set up in the United Kingdom in 1982 by parents of children born with oesophageal atresia and tracheo-oesophageal fistula in order to share information

Calculation of feeding score*

These questions were asked in relation to both milk feeds and introduction of solid foods:

- Did your child take a long time to finish a feed?
- Did your child refuse to feed at times?
- Did your child experience coughing or choking during feed times?
- Did your child vomit during or after feeds?

Parents were asked to indicate for each question whether symptoms occurred with (score):

All feeds	6
Most feeds	5
Half of feeds	4
1-2 Feeds/day	3
1-2 Feeds/week	2
Occasional	1
None	0

*Maximum possible score 48.

and advice. Details of early feeding history were requested and parents asked to indicate the frequency with which specified feed related symptoms had occurred (table). Whether or not, and at what age, symptoms had finally resolved were also recorded. This part of the questionnaire was administered to parents of 50 healthy controls who were either children of colleagues, or siblings of children in hospital. The answers to each question were scored according to frequency of symptom (table) and a 'feeding score' calculated for each child in an attempt to quantify feeding difficulty. Parents were asked to provide accurate height and weight measurements and information regarding whether or not an oesophagostomy had been performed. Height for age, and weight for height standard deviation (SD) scores were calculated for all patients in whom height and weight data were recorded.⁸ Finally, part of the questionnaire was left unstructured for parents to outline their management of feeding difficulties.

STATISTICAL EVALUATION

Feeding scores for different groups of patients and controls were compared using the Mann-Whitney U test. Height for age, and weight for height SD scores were compared with the reference population mean using Student's *t* test. Other comparisons between groups were made using the χ^2 test and Fisher exact probability test. Correlations were calculated using Spearman's method.

Results

A total of 124 of the 230 questionnaires were returned (male:female 2:1). Ninety two (74%)

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of the children with a median age of 4.3 years (range 0.5–22.8) had undergone a primary oesophageal anastomosis. Thirty two (26%) initially had an oesophagostomy and gastrostomy, later followed by an oesophageal substitution procedure. The age range in this group was similar to the primary anastomosis group: mean age 5.6 years (range 1.3 to 22.3; $p=0.3$). The median age at closure of oesophagostomy was 1 year (range 0.1 to 2.5). Fifty replies were obtained from control children, median age 4.5 years (range 0.6 to 12.0).

FEEDING IN HOSPITAL

Primary anastomosis group

Half the parents reported that nursing staff always allowed them to give feeds when they visited hospital but 10 (11%) were never permitted to do so. Forty six mothers (50%) breast fed their infants for a median duration of three months (range two weeks to 21 months). Fourteen (15%) were discouraged from attempting to breast feed and only two rejected this advice.

Oesophagostomy group

Two thirds of parents were always permitted to give feeds when they visited hospital and only two (6%) never allowed. Among the 32 children with an oesophagostomy, all but five had sham feeds at most feed times and only one patient was never sham fed. Compared with the primary anastomosis group, significantly more mothers of children in the oesophagostomy group (11 (34%); $p=0.02$) felt that they were discouraged from breast feeding. Despite this, a similar proportion (12, 38%) did breast feed. The median duration of breast feeding was 2.5 months (range one week to seven months), which was not significantly different from the primary anastomosis group.

Insufficient milk supply was the most common reason for giving up breast feeding. No mother reported inherent difficulties in feeding a child with an oesophageal repair or oesophagostomy as the reason for stopping.

General advice

A minority (45%) of parents were warned before hospital discharge about possible feeding problems and only one third of these received specific advice on management of meal times. Ward nurses were the most frequent source of advice, followed by doctors. Most commonly mentioned was the possibility of choking during feeds, and that feeds were best given slowly. However, only one parent reported being told what to do should this problem occur. Eight (6%) parents discussed feeding with a hospital dietitian.

SPECIFIC FEED RELATED DIFFICULTIES

Control group

The median age at introduction of solid food

was 4 months (range 2 to 7 months) and for solid food containing lumps, 8 months (range 5 to 16 months). The following feed related symptoms were reported to occur with two or more milk feeds a day: slow to feed, six (12%) children; coughing or choking with feed, three (6%); vomiting, four (8%); and feed refusal, five (10%). The prevalence of these symptoms in relation to introduction of solid feeds was considerably reduced, being 4%, 2%, 2%, and 4% respectively. By 1 year of age, all symptoms had resolved in 37 (74%) children, and 45 (90%) children aged 2 or more years were completely symptom free.

Primary anastomosis group

The median age at introduction of solid foods was 6 months (range 1.5 to 30 months) and solids containing lumps, 12 months (range 2 to 54 months). The introduction of solids was significantly delayed compared with the control group ($p<0.0001$). During two or more milk feeds each day, over half the children 56 (61%) were considered by parents to be slow to feed, almost one third (29, 32%) had episodes of choking or coughing, 16 (17%) vomiting, and 18 (20%) feed refusal. The numbers were similar during introduction of solids: 48 (52%) were slow to feed, one third (29, 32%) experienced coughing or choking, 15 (16%) vomiting, and 15 (16%) refused to take feeds. Compared with the control group the prevalence of milk feed refusal or vomiting was not significantly different ($p>0.1$) while being slow with feeds ($p<0.001$) and coughing or choking with milk ($p=0.0002$) were much more common. All problems related to solid foods were significantly more common than in the control group: food refusal ($p=0.02$), taking a long time to feed ($p<0.0001$), coughing and choking ($p<0.0001$), and vomiting ($p=0.007$). Of the 88 children followed up for one year, only 18 (20%) were free of these feed related symptoms, while among 21 children followed up for seven years, 12 (57%) were symptom free.

Oesophagostomy group

The median age at introduction of solid food was 12 months (range 3 to 24 months), significantly later than in the control group ($p=0.0003$), and solid food with lumps 18 months (range 9 to 48 months). Both blended solids and solids with lumps were introduced significantly later than in the primary anastomosis group ($p=0.001$; $p=0.04$). The frequency with which specific feed related symptoms occurred (after closure of oesophagostomy) during at least two feeds each day were similar to those seen in the primary anastomosis group. For milk feeds the figures were: 12 (38%) slow to feed, six (19%) coughing or choking, 10 (31%) vomiting, and seven (22%) feed refusal. Significantly fewer children were slow to take milk feeds ($p<0.05$) than in the primary anastomosis group. For solid feeds the proportion of children with feed related symptoms were: 16 (50%) slow to feed, nine (28%) choking, 10 (31%) vomiting, and six (19%) refusal. Comparing symptoms during milk

feeds with the control group, feed refusal and coughing were not significantly different, though taking a long time to feed and vomiting were both more common after oesophagostomy ($p < 0.01$). All symptoms related to solid feeds were significantly more common than among controls: food refusal ($p = 0.04$), slow with meals ($p < 0.0001$), coughing and choking ($p = 0.0007$), and vomiting ($p = 0.0002$). At 1 year of age no children were completely free of these feed related symptoms, while eight (66%) out of 12 followed up for seven years were asymptomatic.

Troublesome foods

Difficulty swallowing certain types of foods was reported by 24 (26%) of the primary anastomosis group compared with two (6%) of the oesophagostomy group ($p < 0.01$). Many other children were avoiding particular foods for the same reason. The most frequent offenders were similar in each group: meat (37% patients), apple (23%), bread (23%), oranges (14%), and raw vegetables (12%). A further 38 types of food were listed but many items only by one or two families.

GROWTH

Primary anastomosis group

Height and weight data were provided for 73 children of whom 10 were stunted (height for age > 2 SDs below the mean), seven wasted (weight for height > 2 SDs below the mean), and two both stunted and wasted. The mean (SD) height for age SD score was -0.5 (1.8) and mean (SD) weight for height SD score -0.4 (1.6). The group was therefore significantly growth retarded compared with normal population standards for both height for age and weight for height ($p = 0.02$; $p = 0.04$).

Oesophagostomy group

Anthropometric data was provided for 27 children in this group of whom nine were stunted, two wasted, and two both stunted and wasted; this is a significantly higher proportion than in the primary anastomosis group ($p < 0.05$). The mean (SD) height for age SD score was -1.78 (1.7) and the mean (SD) weight for height SD score -1.1 (0.9); both were significantly below the normal population ($p < 0.0001$) and the primary anastomosis group ($p = 0.002$; $p = 0.01$). The prevalence of growth retardation did not decrease with increasing age in either group.

FEEDING SCORE

The median feeding score for the primary anastomosis group was 16 (range 0 to 42), and for the oesophagostomy group 13 (0 to 48). No significant differences in scores were found comparing either each group, or growth retarded, with normally grown children. Feeding scores did not significantly correlate with height for age or weight for height SD scores.

OESOPHAGEAL DILATATIONS

Among the primary anastomosis group 48 patients had been admitted to hospital for elective oesophageal dilatation while 38 had been admitted as emergencies with food stuck in the oesophagus. From the oesophagostomy group 12 underwent elective dilatations of the oesophageal anastomosis and 10 were admitted for emergency oesophagoscopy. Of the patients admitted as emergencies, five were found to have impacted foreign bodies, and food residue were retrieved from the others. Meat was the most common ($n = 20$), followed by apple ($n = 10$), carrot ($n = 7$), and sausage ($n = 6$). The overall proportion of patients in each group having oesophageal dilatations was not significantly different ($p > 0.05$).

SOURCES OF ADVICE FOR PARENTS

Only 14 (11%) of parents reported discussing feeding problems with hospital medical, surgical, and nursing staff; most turned to friends, other members of TOFS, general practitioner, or health visitor. One third of parents had discussed feeding problems during follow up with a hospital dietitian, although a further 57 (46%) indicated that they would have liked to have had this opportunity. Hospital staff were the source of information regarding the existence of the support group for 46 (37%) of parents.

MANAGEMENT OF FEEDING PROBLEMS BY PARENTS

Some parents stated that feeding difficulties dominated their lives and many expressed feelings of isolation and helplessness. The importance of patience, coupled with optimism about the final outcome, was often emphasised.

Sham feeding and gastrostomy feeds

Sham feeding was regarded as an important way of facilitating the return to normal feeding once oesophageal substitution was performed. Almost half of families considered the extra cost to be significant and four had successfully applied to the Department of Health and Social Security for assistance. One parent had designed a stand to which the gastrostomy feed dispenser could be attached leaving both hands free to sham feed the baby. An adjustable gate clamp on the gastrostomy tube regulates the flow of milk. Sham feeding can be a messy business and a towelling nappy or absorbent paper padding around the neck was used to protect the skin; stoma nurses had been useful sources of advice regarding skin care for some patients. Flushing the gastrostomy tube with water after a feed helped prevent blocking and securing the spigot in place with sticky tape can prevent it from becoming dislodged and allowing reflux of stomach contents up the tube. Tucking the gastrostomy tube back into the babies clothing prevents its accidental removal; 'all in one' towelling romper suits are useful garments in this respect.

Meal times

Thirty two percent of parents commented that a food blender was an essential item of equipment; 60 (48%) stressed the importance of keeping babies relatively upright when feeding. Taking time over meals and not attempting to force feed a child were seen as most important, together with the inclusion of the child within the family group at meal times. The necessity of variety in diet was also emphasised. Initially, solid foods were liquidised and lumpy food gradually introduced progressing from finely minced, coarsely minced, to increasingly large lumps. Casseroles or other dishes with plenty of juices rather than dry foods were preferred. Some parents found confectionary (for example, white chocolate) or savouries that melt in the mouth (for example, 'Wotsits') useful for teaching their child to take solids without provoking symptoms.

Choking

Hurrying over food was regarded as a frequent antecedent of choking and a liberal fluid intake during meals as preventative. In the event of acute dysphagia or choking, parents advocated staying calm and back slapping, giving a drink, or inducing vomiting as means of dislodging food. Once the choking episode was over and the child fully recovered it was important to carry on with the rest of the meal.

Discussion

Despite the fact that parents of symptomatic patients are probably more likely to join a support group than those of asymptomatic children, this study has confirmed that feeding difficulties are a major problem after repair of oesophageal atresia. Approximately one third of patients in our survey had severe symptoms such as coughing, choking, vomiting, and refusal at least twice a day in the first year of life, significantly more than control subjects. While the proportion of symptom free patients increased with length of follow up (after seven years two thirds of patients in both groups were symptom free), nearly one third of children over the age of 7 continued to report symptoms, principally dysphagia associated with certain types of food. Initially these symptoms were a source of great concern to parents and had considerable impact on family life.

In addition, anthropometric data reported by parents suggested a worryingly high prevalence of growth failure (32 out of 100 patients for whom height and weight data were provided) with both groups being significantly below the reference population means for the height for age and weight for height. Only six children had other medical conditions that might have contributed to growth failure. Whereas parental reporting of height and weight is unlikely to be accurate, other studies have suggested a similar prevalence of growth failure after repair of oesophageal atresia.^{2 9-11} The oesophagostomy patients were significantly less well grown than the primary anastomosis group (height for age $p=0.002$, weight for height $p=0.01$), which may reflect greater periods of time in hospital or

more refractory feeding difficulties. We did not find a decrease in the proportion of growth retardation with increasing age, suggesting that poor feeding (or whatever other factors might be adversely affecting nutritional state) may have long term effects on growth.

Failure to find a significant negative correlation between 'feed scores' and indicators of nutritional state may reflect both inaccuracy of parental height and weight reporting and the fact that the 'feed score' gives a static measurement of feeding difficulties in relation to introduction of milk and solid feeds and does not take into account overall duration of symptoms.

As an indicator of malnutrition growth requires careful monitoring during follow up.¹² In a recent long term study of patients born with oesophageal atresia it is encouraging that all were found to be normally grown adults.³ Follow up information was available for only 50% of patients operated on over a given period, however, and, as chronic malnutrition and growth failure may affect mortality, nutritionally compromised patients might have been among the 50% who either did not survive childhood or were lost to follow up for other reasons.

Parents evidently find difficulty in dealing with feeding problems and yet may be offered little useful advice.⁴ Breast feeding need not be discouraged, and before discharge from hospital, feeding problems and their management should be fully discussed. A timetable for weaning should be formulated including a plan for graded introduction of different consistencies of solid foods over a period of several months. The fact that each child is different should be highlighted as some have minimal or no difficulties. Although such discussion may take place between parents and nursing or medical staff, dietitians should be involved when possible. During follow up only a third of parents were able to meet a dietitian, although over half the remainder indicated that they would have taken advantage of such contact if offered. Consultation with a dietitian might also help reduce the proportion of parents (31%) dissatisfied with the diets provided on the ward during periods of admission to hospital.

Food 'sticking' can be the result of disordered oesophageal motility and will clear spontaneously or after a drink. Persistent and frequent symptoms should raise the possibility of a stricture and oesophagostomy may be necessary for full assessment. Routine oesophagoscopy and anastomotic dilatation is unnecessary in many children. Choking probably results from aspiration either secondary to disordered oesophageal motility,¹³ or after a food bolus has become lodged. Asphyxia is therefore unlikely to occur and reassurance together with a drink will be all that is required. Choking and vomiting can also be indicative of gastro-oesophageal reflux, which is common after repair of oesophageal atresia and sometimes requires antireflux surgery.¹⁴ Oesophagitis associated with gastro-oesophageal reflux can lead to food refusal or reluctance to feed and should then be suspected even in the absence of vomiting.¹⁵ Twenty four hour

oesophageal pH monitoring is a valuable diagnostic tool in this context and may also help predict the need for further surgery.¹⁶

Feeding problems can come to dominate the lives of parents who may feel particularly helpless when denied one of their important parenting roles by a child unable or unwilling to eat. Whereas optimism in the long term is justified, support and encouragement are required in the early stages. This study indicates areas of management that require closer attention by staff based both in hospital and the community, and, through borrowing from the experiences of parents themselves provides practical advice for those caring for children who have undergone surgery for oesophageal atresia and tracheo-oesophageal fistula.

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Urinary growth hormone excretion as a screening test for growth hormone deficiency

J M Walker, P J Wood, S Williamson, P R Betts, A J Evans

Abstract

Overnight urinary growth hormone secretion was measured by an immunoradiometric assay incorporating commercially available reagents, in 41 normal prepubertal school-children from three age groups: 3-5 years, 6-7 years, and 9-10 years. There was no significant difference between the groups expressing the results as total $\mu\text{U}/\text{specimen}$ and so they have been combined to provide a prepubertal reference range of 2.25-10.50 $\mu\text{U}/\text{night}$. Prepubertal children with growth hormone deficiency who had not been receiving growth hormone treatment for two days had overnight urinary growth hormone concentrations well below this range. Urinary growth hormone was assayed in 49 children undergoing investigation for short stature with conventional provocative testing, and those shown to have growth hormone deficiency had correspondingly low overnight urinary growth hormone concentrations. There was, in addition, a strong correlation between overnight urinary growth hormone concentrations and peak serum response to provocation. This simple urine assay may provide a useful screening test for growth hormone deficiency.

Secretion of growth hormone from the anterior pituitary gland is pulsatile and greatest during slow wave sleep.¹ Screening tests for growth hormone deficiency in current use are based on this observation, and therefore require overnight tests. Alternatively, secretion during the day can be stimulated by drugs. Both types of test require repeated blood sampling from an indwelling cannula, are time consuming, are expensive in terms of manpower and bed occupancy and, above all, are unpleasant and potentially dangerous. An alternative would be the measurement of urinary growth hormone concentration, which would assess integrated growth hormone secretion. Samples could be collected at home, which would have both physiological and psychological advantages. In the past growth hormone assays lacked the sensitivity and specificity to measure accurately the concentration of growth hormone in urine, which is only approximately 0.01% of that in serum.^{2,3} In recent years, however, methods have improved and several immunometric methods have been described that use either enzyme⁴ or ¹²⁵I tracers.⁵⁻⁷

We describe the application of an immunoradiometric assay (IRMA) that uses an adapted commercially available kit, to derive a reference range for urinary growth hormone, to validate

the assay, and to establish the correlation between urinary growth hormone excretion and serum response.⁸

Patients and methods

Timed overnight collections of urine were obtained from three groups of children. Group 1 comprised healthy local primary school-children with heights between the 3rd and 97th standard centiles.⁹ The children were from three age ranges; 3.3 to 4.9 years ($n=16$), 5.8 to 7.0 years ($n=12$), and 9.3 to 10.0 years ($n=13$). All were prepubertal, Tanner stage 1.⁹

Group 2 comprised 14 prepubertal children in the age range 5.8 to 18.2 years who were attending the growth clinic at this hospital for treatment of growth hormone deficiency. They had been diagnosed because at least two conventional provocation tests had shown serum concentrations of less than 20 mU/l. All had normal renal function, serum was negative for growth hormone antibodies, and they had not been receiving treatment for two days.

Group 3 comprised all prepubertal children in the age range 3.7 to 14.6 years ($n=49$) admitted over a 15 month period for investigation of short stature by conventional provocation tests. Five of these children were highly likely to have growth hormone deficiency, as they had typical clinical features or causative features such as cranial irradiation or a craniopharyngioma.

Nine children in group 2 and 14 in group 3 were older than the upper limit set in defining the reference range, but all were prepubertal Tanner stage 1.⁹ Those from group 3 who were more than 10 years old were primed with sex steroids before provocation testing.

The urine samples were collected into plain plastic bottles and transported to the laboratory on the day of collection. Aliquots were taken from the measured urine volume and mixed with bovine serum albumin (1 g/l) and sodium azide (1 g/l) before storage at -20°C until assayed. A separate aliquot was taken for estimation of creatinine concentration using the Jaffé method on an autoanalyser (Technicon Ltd).

ASSAY⁸

The assay used the reagents of the Boots-Celltech kit for estimation of serum growth hormone concentration. Before assay the urine was thawed and dialysed overnight against a phosphate/azide buffer (50 mm l/phosphate, pH 7.0, containing sodium azide 1 g/l). The growth

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hormone was then extracted overnight on to a monoclonal antibody coupled to solid phase particles that were then centrifuged to remove excess urine. Iodinated antibody was added and after 3.5 to 5 hours the resulting sandwich of solid phase linked antibody, urinary growth hormone, and iodinated antibody was separated from excess label with a standard 'Sucrosep' sucrose separation.

STATISTICAL ANALYSIS

The results were transformed logarithmically as the data were not normally distributed, and the non-parametric Wilcoxon rank sum and Mann-Whitney U tests were used to assess the significance of differences between groups. Correlation coefficients were calculated using the least squares regression analysis.

Results

Group 1—normal children: results were plotted for each of the three age groups with the 95% confidence intervals expressing the urinary growth hormone concentrations as total $\mu\text{U}/\text{night}$ (graph A) and $\mu\text{U}/\text{mmol}$ urinary creatinine (graph B) (fig 1). For clarity the y axes are logarithmic. There was no significant difference between sexes and no correlation between urinary growth hormone and height within these age bands. In graph A there was no significant difference between the three age groups ($p>0.05$) but when the results were expressed as $\mu\text{U}/\text{mmol}$ urinary creatinine (graph B) the difference between the youngest and the oldest children was significant ($0.05<p<0.01$). Expressing the results/unit time gave no better discrimination between normal and short children than the simple total $\mu\text{U}/\text{night}$. Thus these latter results were combined to provide a reference range (95% confidence intervals) for normal prepubertal children aged more than 3 years of 2.25–10.50 $\mu\text{U}/\text{night}$. This was the reference range used in the subsequent studies.

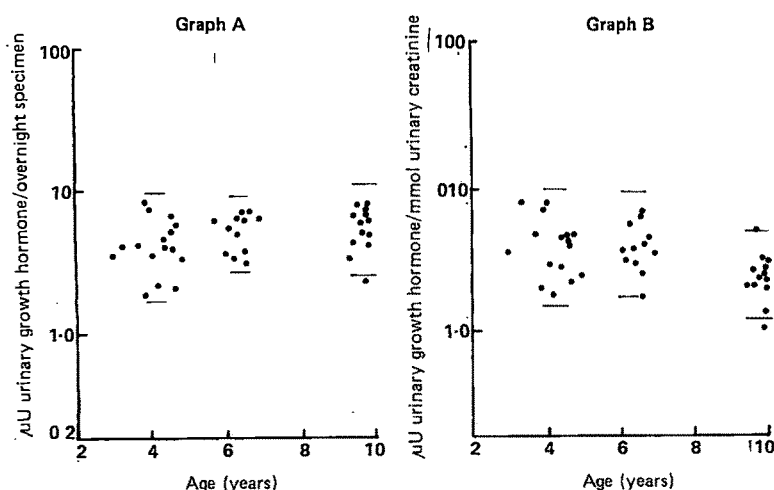


Figure 1 Overnight urinary growth hormone concentrations expressed as $\mu\text{U}/\text{night}$ (graph A) and $\mu\text{U}/\text{mmol}$ urinary creatinine (graph B) in three age groups of prepubertal children of normal stature. The horizontal bars represent the 95% confidence intervals.

Group 2—prepubertal children with growth hormone deficiency: in all cases the results were well below the reference range and easily distinguished from it (fig 2).

Group 3—prepubertal children with short stature: results from 49 children who underwent a sleep test and a clonidine or insulin stress test, or both, are shown in fig 3. All those children who were subsequently found to have growth hormone deficiency (defined as a serum growth hormone concentration of less than 20 mU/l in response to provocation) had correspondingly low overnight urinary growth hormone concentration. This was in obvious contrast to those whose serum response was more than 20 mU/l, who all had urinary growth hormone concentrations within the reference range. The urinary growth hormone excretion in these latter children aged under 10 years was, however, significantly less ($0.01>p>0.001$) than that of the normal schoolchildren.

Fig 4 shows that the correlation between overnight urinary growth hormone excretion and peak serum response to either clonidine or insulin was highly significant ($r=0.64$, $p<0.001$). Again the urinary growth hormone

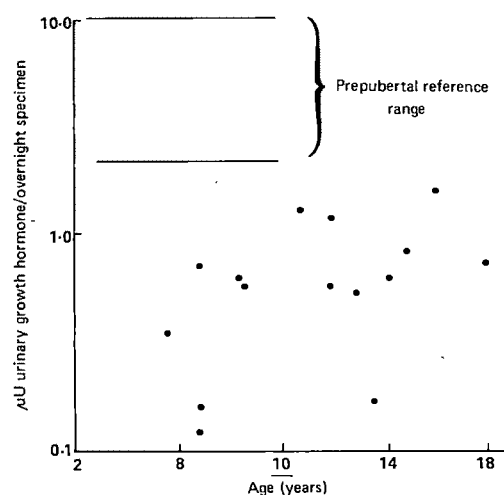


Figure 2 Overnight urinary growth hormone in prepubertal children with known growth hormone deficiency off treatment for two days.

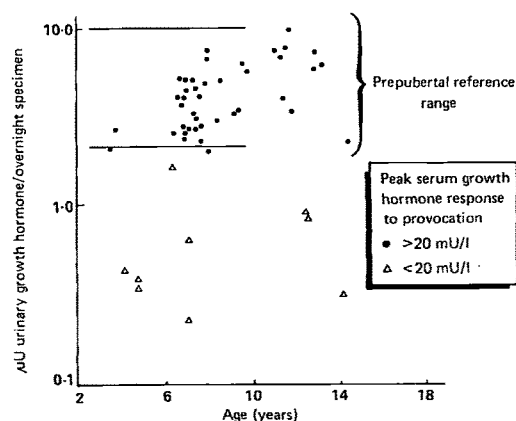


Figure 3 Overnight urinary growth hormone in prepubertal children with short stature.

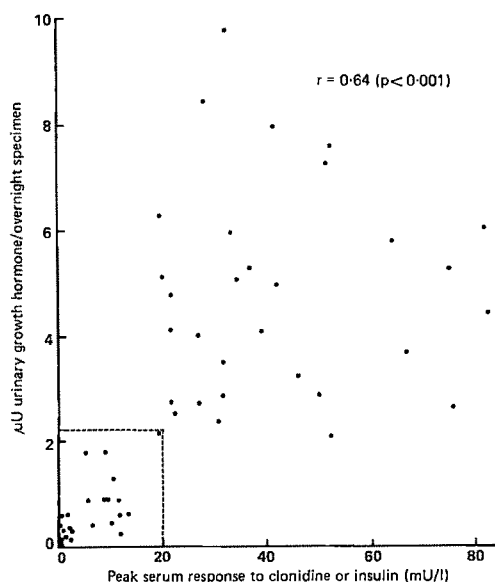


Figure 4 Correlation between overnight urinary growth hormone and peak serum growth hormone response to provocation. The dotted lines mark the cut off between normal and abnormal for each of the two variables.

excretion distinguishes those children who had growth hormone deficiency on provocation testing.

Discussion

If this assay is to be a good screening test it has to fulfil certain criteria. Firstly, it should be easily applicable to the appropriate population both in terms of acquisition of samples and laboratory handling. An overnight urine collection is non-invasive and simple to make at home, and thus is ideal for children. Moreover, the results can be expressed simply as $\mu\text{U}/\text{overnight specimen}$ and there seems to be no advantage in calculating the results as a ratio of time or creatinine excretion. Previously reported assays have usually expressed their results by unit of urinary creatinine to compensate for possible inaccuracy of collection,¹⁰ but our results show that this produced the only significant difference between the age groups. This fall in urinary growth hormone/mmol creatinine with age is almost certainly a consequence of the known increase in urinary creatinine with age and body mass.¹¹ Conversely, relating urinary growth hormone to creatinine may produce falsely high concentrations in patients with hypopituitarism, because protein synthesis and creatinine excretion are reduced.

Our assay also has the important advantage of using an adaptation of a commercially available kit. Most other groups have used 'in house' monoclonal antibodies, which few NHS laboratories will have the time, resources, or expertise to produce; many, however, are fully acquainted with Boots-Celltech kits.^{4 5}

Secondly the method needs to be highly sensitive and specific. This assay can detect 0.50 μU of growth hormone and is valid in terms of recovery, parallelism, and precision.⁸

Finally, results must show good discrimination between normal and abnormal subjects. This is

not the first study to show differences in urinary growth hormone excretion between children with normal and abnormal growth. Hashida *et al.*, using a highly sensitive and specific immunoenzymatic assay, reported five patients with hypopituitarism and urinary growth hormone concentrations below their range for normal subjects.¹⁰ In deriving the latter, however, they combined pubertal and prepubertal children (as have other groups^{5 6}) despite the known rise in serum growth hormone in puberty.¹² Recently this rise has also been seen in urinary growth hormone excretion with a peak in stage 4 puberty.⁷ Two other groups have found the mean excretion of urinary growth hormone to be significantly greater in normal children than in those with growth hormone deficiency, but they showed up to 25% overlap between the populations.^{5 6} Neither of these studies used preservatives when storing the samples and one also omitted dialysis.⁵ Both of these steps are considered essential by us⁸ and others,^{3 13} and their omission may affect the sensitivity of the assay, producing less good discrimination especially at the lower end of the range.

The diagnosis of growth hormone deficiency is controversial and there is probably a range of growth hormone secretion, with no clearly defined cut off between normal and abnormal. Tall children become so by secreting more growth hormone and growing faster than short children.¹⁴ This is reflected in the significantly lower, but apparently normal, urinary growth hormone excretion in the children under 10 years old who were of short stature but who did not have classical growth hormone deficiency on provocation testing (fig 3). The trend towards higher urinary growth hormone concentrations in those over 10 years old but still prepubertal, may have been the result of the priming with sex steroids. Some overlap at the bottom end of the range could be anticipated, and indeed a few of the younger children had values at the lower limit. The comparatively large number of children with low urinary growth hormone concentrations is partly explained by our study population containing several children who could be predicted to have growth hormone deficiency. Any overlap may become more obvious when further data are available for analysis, but it would not detract from the potential value of measurement of urinary growth hormone excretion as a screening test.

The positive correlation between peak serum response to provocation and overnight urinary growth hormone excretion (fig 4) confirms that the urine test may be as good as blood tests in identifying children whose growth problems are caused by a relative deficiency of growth hormone. The correlation almost exactly mirrors that in another comparison of a physiological and a pharmacological stimulus to growth hormone release, in this instance a sleep test monitored by electroencephalography with peak response to an insulin stimulation test.¹⁵ The advantages of an overnight urine collection at home need no emphasis.

The results also support the correlation between urinary growth hormone excretion rate

and mean plasma growth hormone concentration, the sum of growth hormone peaks, and the area under the growth hormone curve during overnight secretory profiles.⁷ It does not signify that a high serum concentration produced in response to powerful drugs is associated with faster or better growth. Indeed, the advent of recombinant growth hormone (Gentotropin, Kabi Vitrum) means that an adequate response to provocation does not preclude treatment of a slowly growing child on clinical grounds, especially if 24 hour serum sampling confirms the suspicion of 'neurosecretory dysfunction'.¹⁶ Far commoner, however, in the setting of a general paediatric clinic are short children with anthropometric data indicating possible growth hormone deficiency. A simple screening test to exclude growth hormone deficiency and thus identify the minority of children who require invasive investigations and referral to a regional growth centre would be an important advance and should result in a considerable financial saving; this urinary growth hormone assay may well be that test.

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Absence of effect of dipyridamole on renal and platelet function in diabetes mellitus

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Abstract

We evaluated the effect of dipyridamole (5 mg/kg/day) for 12 months on renal and platelet function in 53 children with insulin dependent diabetes mellitus (IDDM) in a prospective double blind placebo controlled trial. Urine albumin excretion (expressed as the geometric mean albumin to creatinine concentration ratio (UA/UC) was measured every three months throughout the study. At 12 months, the geometric mean UA/UC was no different in diabetic children receiving dipyridamole, 0.60 mg/mmol, when compared with those receiving placebo, 0.87 mg/mmol. Glomerular filtration rate, urinary excretion of retinol binding protein, and N-acetyl- β -D-glucosamidase (NAG), blood pressure, and spontaneous platelet aggregation in response to stirring whole blood did not differ between the two groups at 12 months. Subgroup analysis to include only those children with high UA/UC before entry into the study also failed to show an effect of the drug on UA/UC.

Eleven children had either persistently high UA/UC (n=8: four on dipyridamole, four on placebo) or progression to high UA/UC (n=3: two on dipyridamole, one on placebo). These children had significantly higher urinary excretion of retinol binding protein and NAG, bigger kidneys, and higher diastolic blood pressure both before and after treatment than the remaining 42 children, whereas there was no difference in spontaneous platelet aggregation between the two groups. These observations on the associations between UA/UC and other parameters of renal function suggest that measurement of 'tubular' proteins and diastolic blood pressure as well as UA/UC may contribute to the identification of those at risk of developing nephropathy.

It has been suggested that platelet activation contributes to the pathogenesis of both the macrovascular and the microvascular complications of diabetes mellitus.¹⁻³ Shortened platelet survival,⁴ increased platelet aggregation *in vitro*,⁵ and release of intraplatelet substances^{5,6} have all been reported in adults with established microvascular complications. In those without complications the studies have been conflicting, however, with some^{7,8} but not others⁹⁻¹¹ reporting abnormalities of platelet function. Further evidence linking platelet activation with diabetic nephropathy comes from a study using the specific inhibitor of thromboxane synthetase, UK-38,485, in which 30 patients with microalbuminuria had significantly reduced

urine albumin excretion rates after 16 weeks of treatment with this drug compared with placebo, and albumin rebounded to pretreatment concentrations after its discontinuation.¹²

Dipyridamole, a commonly prescribed antiplatelet drug used in combination with aspirin as an antithrombotic agent,^{13,14} has been reported to reduce urine albumin excretion and to increase platelet survival in different glomerulopathies in both adults and children.^{15,16} In combination with aspirin, it has also been reported to decrease urine albumin excretion in studies of adults with established diabetic nephropathy.¹⁷⁻²⁰ Although it has been proposed that this effect is mediated by a change in platelet function, there is also experimental evidence suggesting that it may reduce proteinuria by causing efferent arteriolar dilatation, with a resulting decrease in hyperfiltration.^{21,22}

The studies undertaken so far have been in patients with established or incipient nephropathy and it is unknown whether these drugs may be effective in the primary prevention of nephropathy. In a previously reported cross sectional study of children and adolescents with insulin dependent diabetes mellitus (IDDM), we observed a small but significant increase in platelet aggregation in whole blood *in vitro* compared with normal children. We also observed increases in both urine albumin excretion and glomerular filtration rate and noted a threshold association between the two, those children with high urine albumin excretion also having a high glomerular filtration rate and larger than average kidneys.²³ We now report the results of a placebo controlled trial of the effect of dipyridamole taken for 12 months on renal and platelet function in these same children with IDDM. In addition, over this time period, we investigated the evolution of the association between renal and platelet function.

Subjects and methods

SUBJECTS

Sixty children with IDDM were recruited from the diabetic clinics of the Hospitals for Sick Children, London. Their mean (SD) age was 13.1 (3.5) years and the mean (SD) duration of diabetes was 7.0 (4.3) years; there were 33 girls and 27 boys. Two children were receiving anti-convulsant drugs (carbamazepine and sodium valproate); the remainder were receiving no other treatment except insulin and had no significant disease other than diabetes. None of the children had taken aspirin during the two weeks before entry into the trial and all were given oral and written instructions to avoid taking aspirin

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like drugs throughout the trial period. No child had evidence of urinary tract infection or renal abnormality on ultrasound at entry into the study.

TRIAL DESIGN

The trial was a double blind placebo controlled study with the randomisation stratified for urine albumin excretion. The primary end point was to ascertain whether dipyridamole modified urine albumin excretion in childhood diabetes. Secondary endpoints were to observe whether there was any effect of the drug on platelet function and other indices of renal function.

We wished to detect a 30% difference between treatment and placebo groups at 12 months, assuming a standard deviation of 35%. To give 80% power at the 95% level of significance 20 patients per group were required.

Urine albumin excretion was measured within the three months before, and again at entry to the trial. In addition, urinary excretion of retinol binding protein, N-acetyl- β -D-glucosaminidase (NAG), renal size, blood pressure, glycated haemoglobin (HbA_{1c}), and platelet aggregation were measured in all children at entry to the trial. Measurements of glomerular filtration rate were available on 41 children only. The children were then randomly allocated to receive either dipyridamole, 5 mg/kg body weight/day, or matching placebo in a twice daily dosage. Unmarked preparations were provided by Boehringer Ingelheim and the randomisation schedule was kept in the hospital pharmacy. All children were followed up by the same investigator and neither she nor the patients were aware of the treatment each child was receiving.

Measurements of blood pressure, pubertal state, urine albumin excretion, 'spontaneous' platelet aggregation, and HbA_{1c} were made at intervals of three months. In addition, renal size and tubular proteins were measured at completion of the study at 12 months, and glomerular filtration rate was remeasured in the 41 children initially studied. Final estimations of blood pressure, HbA_{1c}, urine albumin excretion, and platelet aggregation were undertaken three months after discontinuing the drug.

The study had the approval of the ethics committee of the Hospital for Sick Children, Great Ormond Street, London.

ANALYTICAL METHODS

Urinary albumin (UA) was measured by radioimmunoassay using a commercial kit (Diagnostic Products (UK) Ltd, sensitivity 0.5 mg/l, intra-assay and interassay variability 4% and 5% respectively). Urinary retinol binding protein (URBP) was measured by an enzyme linked immunosorbent assay (ELISA) technique using rabbit antisera (Dako Ltd).²⁴ Urinary NAG (UNAG) was measured by an automated colorimetric method using p-nitrophenyl-N-acetyl- β -D-glucosamide (Sigma Chemical Co) as substrate.²⁵ Urine creatinine (UC) was measured by the Jaffé reaction. Urinary excretion of protein was expressed as the geometric mean of the ratio of the protein concentration to

that of creatinine in two consecutive overnight urine samples (UA/UC (mg/mmol), URBP/UC (μ g/mmol), UNAG/UC (μ mol p-nitrophenyl (pnp) hour/mmol)). The upper limit of normal was defined as the upper 95% tolerance limit in 45 normal children calculated from log data. This was 1.17 mg/mmol for UA/UC, 15.0 μ g/mmol for URBP/UC, and 25.0 μ mol pnp hour/mmol for UNAG/UC.²⁶ We have previously shown that a UA/UC value of 1.17 mg/mmol is equivalent to a urine albumin excretion rate of 8.2 μ g/min/1.73 m² surface area.²⁷

Glomerular filtration rate was measured during a constant infusion of 51-chromium edetic acid (⁵¹Cr-EDTA) under conditions of water diuresis by standard renal clearance techniques with spontaneous voiding of urine. The upper 95% tolerance limit in 15 adult controls was 135 ml/min/1.73 m² surface area.²³

Renal length was measured by ultrasonography with the child in the prone position and was related to normal data for right and left kidney lengths plotted against body height.²⁸ The standard deviation (SD) score for each kidney was calculated from the formula: SD score = (measurement - mean)/SD. Data on the diabetic children was expressed as the mean of the right and left kidney length SD scores, compared with these normal published sonographic growth charts.²⁸

Blood pressure was measured using a random zero sphygmomanometer with the child seated. Results are presented both as raw data and SD scores calculated from the American Task Force Data for blood pressure in normal children.²⁹

HbA_{1c} was measured by electrophoresis (normal range 5–8%).

Platelet aggregation was measured in whole blood in response to stirring using the Ultraflo 100 whole blood platelet counter.³⁰ A sample of 5 ml blood was taken into a polypropylene syringe using a 19 gauge needle and immediately transferred into a polystyrene tube containing 0.5 ml 3.8% trisodium citrate dihydrate. A 0.5 ml aliquot was then stirred in a plastic tube at 1000 rpm at 37°C. A 20 μ l aliquot was taken two minutes after stirring had started, and immediately fixed with 40 μ l of formalin-edetic acid solution to prevent further aggregation or disaggregation before counting. All samples were counted in triplicate and the mean taken. Aggregation was expressed as the percentage fall in platelet count at two minutes compared with the count in an aliquot taken immediately before stirring.³⁰ All experiments were performed between one and three hours after venepuncture as, in agreement with Saniabadi *et al*, we have found that aggregation after venepuncture increases over the first hour and then stabilises.³¹ The upper 95% tolerance limit for spontaneous aggregation in 26 normal children was 27% at two minutes.²³ Aggregation in response to platelet activating factor was also measured at the three month visit. After one minute stirring, 4 μ l of 500 nM platelet activating factor was added to 500 μ l whole blood (making a final concentration of 4 nM platelet activating factor) and aliquots taken as described above at 15 seconds, 30 seconds, one minute and two minutes later.

STATISTICAL METHODS

Withdrawals from the study were excluded from the analysis; all occurred in the first three to six months.

Before analysis, it was decided that the following covariates should be considered: baseline values, age, Tanner puberty stage in three groups (stage 1, stages 2 and 3, stages 4 and 5), duration of diabetes, and sex. Age and duration of diabetes were particularly important because the children treated with dipyridamole were on average 1.7 years older and had a disease duration of 2.6 years longer than those treated with placebo.

All covariates were tested with the primary and secondary end points; only age and baseline values indicated a consistent effect and hence only these were included in the final model.

Analysis of variance tests were used at each visit, but significance was only attached to the 12 months result. In cases where UA/UC data ($n=5$) or platelet aggregation data ($n=4$) at 12 months were missing, the previous recorded reading at nine months was used. UA/UC, URBP/UC, and UNAG/UC were log transformed before analysis; all tests indicated that the data (transformed as appropriate) did not deviate appreciably from normality.

Results

WITHDRAWALS AND SIDE EFFECTS

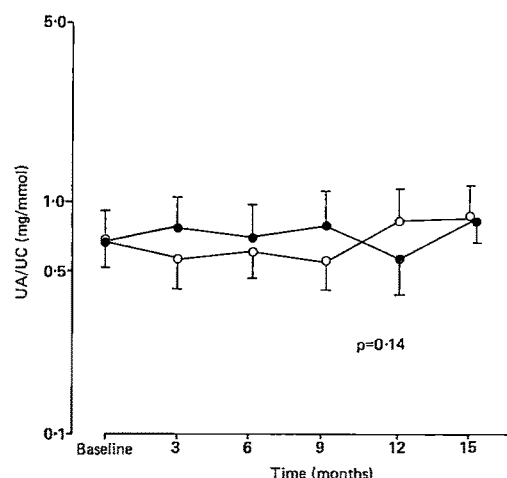
Seven children withdrew from the study (four defaulted and three developed headaches: two on dipyridamole and one on placebo). Ten others reported mild headaches (four on dipyridamole and six on placebo); a temporary reduction in dose followed by a gradual increase back to 5 mg/kg/day alleviated headaches in these children regardless of treatment.

BASELINE DATA

Excluding withdrawals, the 28 children in the placebo group were younger and had a shorter duration of diabetes than the 25 children taking dipyridamole (table 1). The results of UA/UC, tubular protein excretion, blood pressure, HbA_{1c}, glomerular filtration rate, and platelet aggregation at baseline were similar in both groups.

URINE ALBUMIN EXCRETION

There was no evidence of treatment differences over the 15 months. During the first nine months, the placebo group had slightly lower UA/UC, but at 12 months this was reversed and



Geometric mean and 95% confidence intervals (only one shown for clarity) for UA/UC in diabetic children treated with dipyridamole (●) or placebo (○).

those on dipyridamole had a geometric mean (95% confidence interval) UA/UC of 0.60 (0.42 to 0.85) compared with that of 0.87 (0.62 to 1.21) in the placebo group ($p=0.14$). At 15 months, both groups had similar UA/UC (figure). The seven children who withdrew from the trial had UA/UC readings at the time of withdrawal that were similar to those who completed.

Seventeen children had UA/UC values above normal at screening (eight on dipyridamole and nine on placebo). Analysis indicated that those with original high UA/UC tended to maintain higher values throughout the study, but there was no evidence that the treatment worked better in this subgroup (the subgroup treatment interaction ranged from $p=0.09$ – 0.71 for months three to 15).

SECONDARY END POINTS

HbA_{1c} and glomerular filtration rate were similar in both groups throughout the study (table 2). Thirteen children had a high glomerular filtration rate (>135 ml/min/1.73 m², 95% tolerance level in controls) at the beginning of the study (six on dipyridamole and seven on placebo). At 12 months, glomerular filtration rate was lower in these children by 9% (95% confidence interval 4 to 13%) but this difference was the same in both the dipyridamole (9%, 95% confidence interval 2 to 21%) and the placebo treated groups (9%, 95% confidence interval 2 to 15%). Of the four withdrawals who had glomerular filtration rate measurements performed, two had high and two had normal

Table 1 Characteristics of diabetic children who completed the study and withdrawals

	No of children	Age* (years)	Duration of diabetes* (years)	Sex
Children who completed study:				
Dipyridamole	25	13.6 (3.4)	8.2 (4.7)	14M, 11F
Placebo	28	11.9 (3.4)	5.6 (3.3)	11M, 17F
All	53	12.7 (3.4)	6.8 (4.2)	25M, 28F
Withdrawals:				
Dipyridamole	4	14, 15, 16, 18	2, 6, 10, 16	1M, 3F
Placebo	3	12, 16, 18	7, 8, 9	1M, 2F

*For children who completed the study the results are mean (SD).

glomerular filtration rate values at baseline. One child had a glomerular filtration rate of 60 ml/min/1.73 m² at 12 months, having had a glomerular filtration rate of 145 ml/min/1.73 m² at baseline. Her diabetic control was very poor throughout the trial (HbA_{1c} 17–18.8%) and she developed oedema, hepatomegaly, microalbuminuria, and a high URBP/UC between nine and 12 months while taking dipyridamole. As on the residual plot the 12 month glomerular filtration rate value was clearly an outlier, she was omitted from the 12 month analysis for this variable alone.

There was no evidence of a treatment effect on blood pressure, renal size, tubular proteins, or platelet aggregation (table 2). At three months the mean (95% confidence interval) percentage fall in platelet count in response to platelet activating factor at 15 seconds was similar in the dipyridamole treated children, 42.5% (34.7 to 50.3), compared with the children receiving placebo, 39.3% (31.3 to 47.3).

CHILDREN WITH HIGH UA/UC

Twenty four children (13 on dipyridamole and 11 on placebo) had at least one value above normal during the course of the study; three children (two on dipyridamole and one on placebo) progressed from normal UA/UC to high UA/UC, defined as at least three consecutive UA/UC >1.17 mg/mmol; and eight children (four on dipyridamole and four on placebo) had readings persistently above this level. Of these eight children with persistently high UA/UC, four had values consistently above

2.5 mg/mmol (equivalent to a urine albumin excretion rate of 20 µg/min/1.73 m²)²⁷; two were on placebo and two on dipyridamole treatment.

As no significant treatment effects were observed during the trial, data from all 53 patients completing the trial were pooled and the associations between indices examined at baseline and at 12 months. The 11 children with high UA/UC throughout the trial had higher URBP/UC, UNAG/UC, diastolic blood pressure SD scores, and mean kidney length SD scores at both baseline and at 12 months than the rest of the children, irrespective of treatment group (table 3). Although there was a tendency for systolic blood pressure scores to be higher in the children with high UA/UC, the differences were not significant. Glomerular filtration rate was measured at baseline in only six of the 11 children with high UA/UC; values were higher than the rest of the children at baseline. At 12 months, however, one child described above had a dramatic fall in glomerular filtration rate, and the mean glomerular filtration rate in the other five children was not significantly greater than that of the remaining children.

Platelet aggregation results throughout the study were consistently above normal in only one patient. She was taking dipyridamole and had normal UA/UC and glomerular filtration rate throughout the study. If platelet aggregation in the 11 children with persistently high or progression to high UA/UC were compared with the rest of the children, although higher throughout the study, the differences were not

Table 2 Comparison of indices of renal and platelet function in children on dipyridamole compared with placebo. Results at 12 months are adjusted for age and baseline values and are expressed as mean and 95% confidence interval

	Baseline (n=53)	12 Months	
		Dipyridamole (n=25)	Placebo (n=28)
HbA _{1c} (%)	11.8 (11.2 to 12.4)	11.5 (10.7 to 12.3)	11.5 (10.7 to 12.2)
Renal size (SD score)	0.25 (-0.07 to +0.57)	0.12 (-0.3 to +0.54)	0.13 (-0.31 to +0.57)
URBP/UC (µg/mmol)	8.2 (5.9 to 11.2)	14.5 (9.3 to 22.8)	10.9 (7.2 to 16.5)
UNAG/UC (µmol pnp/hr/mmol)	38.1 (28.2 to 50.4)	60.9 (46.3 to 80.0)	63.2 (49.2 to 81.1)
Systolic blood pressure	110 (108 to 113)	113 (109 to 117)	112 (108 to 115)
Diastolic blood pressure	70 (67 to 73)	73 (69 to 77)	71 (67 to 74)
Spontaneous platelet aggregation (% fall at 2 min)	17.9 (15.4 to 20.4)	13.5 (10.6 to 16.3)	12.3 (9.6 to 14.9)
	n=36	n=18	n=18
Glomerular filtration rate (ml/min/1.73 m ²)	129 (123 to 135)	128 (123 to 133)	124 (118 to 129)

Table 3 Comparison of renal and platelet function in children with persistently high or progression to high UA/UC and those with normal UA/UC. Results expressed as mean (SEM) or geometric mean (95% confidence interval) from log data.

		High UA/UC (n=11)	Normal UA/UC (n=42)	p Value
Age (years)		14.1 (0.93)	12.4 (0.52)	0.11
Disease duration (years)		7.5 (1.10)	6.7 (0.66)	0.54
Sex		9F, 2M	19F, 23M	0.07
HbA _{1c} (%)	Baseline	13.1 (0.60)	11.5 (0.30)	0.02
	12 Months	13.4 (0.80)	11.0 (0.30)	0.005
Renal size (SD score)	Baseline	1.01 (0.38)	-0.05 (0.15)	0.007
	12 Months	1.25 (0.39)	-0.20 (0.17)	0.0001
URBP/UC (µg/mmol)	Baseline	16.4 (12.4 to 21.7)	9.2 (6.8 to 12.4)	0.002
	12 Months	30.6 (10.4 to 36.0)	6.6 (4.8 to 9.1)	0.004
UNAG/UC (µmol pnp/hr/mmol)	Baseline	67.3 (36.0 to 126.0)	33.0 (24.7 to 67.8)	0.07
	12 Months	95.7 (70.5 to 130.0)	56.0 (43.9 to 71.3)	0.004
Systolic blood pressure (SD score)	Baseline	0.26 (0.17)	0.16 (0.11)	0.62
	12 Months	0.49 (0.26)	0.10 (0.13)	0.16
Diastolic blood pressure (SD score)	Baseline	1.02 (0.22)	0.35 (0.12)	0.007
	12 Months	1.02 (0.27)	0.40 (0.12)	0.04
Platelet aggregation	Baseline	22.3 (3.3)	16.6 (1.6)	0.11
	12 Months	10.9 (1.6)	13.7 (1.3)	0.37
Glomerular filtration rate	Baseline	142.7 (5.1)	126.3 (3.4)	0.007
	12 Months	130.4 (6.8)	124.9 (2.9)	0.48

significant (table 3). There was a tendency for platelet aggregation results to be lower at the end compared with the beginning of the trial in both groups and there was no evidence of dipyridamole affecting platelet aggregation.

Discussion

In this study we observed no effect of dipyridamole on urine albumin excretion in children and adolescents with IDDM, irrespective of whether urine albumin excretion at the start of the study was normal or high. In addition there were no appreciable changes in glomerular filtration rate, blood pressure, or tubular proteins in the treatment group compared with those taking placebo. The treatment and placebo groups were well matched for degree of metabolic control, and age was controlled for in the analysis.

The effects of dipyridamole on renal function are not understood; experimentally it has been reported to decrease the filtration fraction and cause efferent vasodilatation,²¹ possibly mediated via intrarenal adenosine.²² This could result in a decrease in proteinuria, which may be independent of an antiplatelet action.³² Dipyridamole has been reported to reduce proteinuria in a variety of both childhood and adult renal disease, but these studies were uncontrolled.^{16, 33} In a placebo controlled study of antiplatelet treatment in membranoproliferative glomerulonephritis, dipyridamole in combination with aspirin stabilised the glomerular filtration rate but interestingly, had no effect on proteinuria.¹⁵ In diabetic nephropathy most studies have been undertaken on adults with established nephropathy and in all, dipyridamole was taken in combination with aspirin. Thus Hopper *et al* reported a decrease in proteinuria but also a decrease in creatinine clearance in 16 adults with established diabetic nephropathy; the study had a crossover design and patients took the active drugs for a period of six weeks.¹⁷ Christopher *et al* reported a decrease in albumin excretion and stabilisation in glomerular filtration rate over a two year period in seven adults with established diabetic nephropathy compared with six who took placebo.¹⁸ Most recently, Donadio and colleagues reported the results of treatment with aspirin and dipyridamole for 4.3 years on urine albumin excretion, glomerular filtration rate, and platelet survival in 28 diabetic adults with established nephropathy.²⁰ They reported that seven of the 28 patients had a decrease in urine albumin excretion and stabilisation of renal function, with decline in glomerular filtration rate occurring at the rate of 6 ml/min/year in this group. It is unclear, however, how these seven patients were selected for separate analysis, which appears to have been undertaken retrospectively rather than prospectively. In addition, the study was uncontrolled and although not significant, basal rates of urine albumin excretion were lower and glomerular filtration rate was higher in patients who 'responded'. Platelet survival improved and urinary thromboxane β_2 excretion decreased on treatment, but not necessarily in those patients

who had a more stable renal course. In a subgroup of patients treated at the beginning of the study with dipyridamole alone, the decrease in thromboxane β_2 over a four week period was not significant. The conclusion that a combination of aspirin and dipyridamole reduces urine albumin excretion and stabilises renal function in diabetic nephropathy still requires confirmation.

In the only other study to investigate the effect of dipyridamole on renal function earlier in diabetes, the drug was again taken in combination with aspirin. Hopper *et al* measured the effect of a combination of aspirin and dipyridamole on exercise induced albuminuria in adults early in the disease.³⁴ Only six patients were studied, however, and albumin excretion rates in the treated group were significantly reduced only when expressed as ratios of results collected after exercise to those collected immediately before exercise.

The role of platelets in the pathogenesis of diabetic nephropathy is unclear. Whereas there are reports of increased platelet activation in the presence of established microvascular complications,⁴⁻⁶ the role of platelets in the pathogenesis of complications is much less secure. Two recent studies using sensitive techniques failed to show any abnormalities in platelet aggregation, or excretion of urinary metabolites of thromboxane synthesis in diabetic adults without evidence of microvascular complications.^{9, 10} Hendra *et al* observed no differences in platelet aggregation in platelet rich plasma or whole blood diabetic adults with short disease duration.¹⁰ Platelet aggregation in whole blood has the advantage of not requiring centrifugation, which may result in loss of the more active platelets as well as removing red and white cells which can liberate platelet active substances.^{30, 35} Indeed, strong circumstantial evidence suggests that 'spontaneous' platelet aggregation in stirred whole blood is a reflection of the aggregating effect of adenosine diphosphate released by erythrocytes by mechanical stirring.³⁵ Dipyridamole, which requires high concentrations to inhibit platelet aggregation in platelet rich plasma,^{36, 37} has been found to inhibit both spontaneous aggregation and aggregation in response to platelet activating factor in whole blood in vitro.³⁸⁻⁴⁰ In this study, however, we were unable to detect any differences in either spontaneous or platelet activating factor induced aggregation in diabetic children taking dipyridamole compared with those on placebo treatment. The children had taken their morning dipyridamole three to six hours before having blood taken and it may be that blood concentrations were no longer in the therapeutic range. Mahony *et al*, however, have suggested that because of the enterohepatic circulation, there is no need for dipyridamole to be taken more frequently than twice daily.⁴¹ The other possible explanation is that the aggregation experiments were performed too long after venepuncture. Saniabadi *et al*, using a rolling rather than stirring model to induce 'spontaneous' aggregation, observed significant inhibition by dipyridamole only if the aggregation was initiated within three minutes after venepuncture.³¹

In this study there were a total of 11 children who either had persistently high UA/UC or progressed to high UA/UC. Four of these children had UA/UC equivalent to $>20 \mu\text{g}/\text{min}/1.73 \text{ m}^2$ throughout the study (two on placebo and two on dipyridamole treatment): a value which has been the consensus definition of microalbuminuria. In comparison with the remaining 42 children, the 11 children with high UA/UC had higher HbA_{1c} , bigger kidneys, higher 'tubular' protein excretion rates, and higher diastolic blood pressure both at baseline and 12 months later; the values in the four children with highest UA/UC were even higher for all these parameters. The results for glomerular filtration rate are difficult to interpret because only six of the 11 had this measured; although values were higher in children with high UA/UC at baseline, the difference was not significant at 12 months.

In conclusion, we have shown that dipyridamole taken over a 12 month period has no significant effect on urine albumin excretion, 'tubular' protein excretion, glomerular filtration rate, blood pressure, or platelet aggregation in whole blood in children with IDDM. Children with levels of urine albumin excretion above the normal range also have consistently higher HbA_{1c} , increased tubular protein excretion, larger kidneys, and higher diastolic blood pressure, but no consistent increase in platelet aggregation. Much longer follow up is required to observe whether the values of UA/UC above the normal range but less than $20 \mu\text{g}/\text{min}/1.73 \text{ m}^2$ are predictive for nephropathy, and whether other indices of renal function may contribute to the identification of patients at risk of nephropathy.

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Clinical monitoring of steatorrhoea in cystic fibrosis

M P Walters, J Kelleher, J Gilbert, J M Littlewood

Abstract

In 100 patients with cystic fibrosis the severity of steatorrhoea was assessed by three separate methods. Using chemical faecal fat assay as the gold standard, two other rapid and inexpensive methods were compared with it. The steatocrit method proved unreliable in our hands and gave little indication of the presence or severity of steatorrhoea. The more simple microscopy method was highly sensitive (97%) and only three of 80 patients with steatorrhoea were missed. All patients with severe steatorrhoea (>60 mmol fat/day) were clearly demonstrated. The method is applicable to spot faecal samples and can readily be carried out on an outpatient basis. In centres where faecal fat assays are not available, the simple and cheap microscopic examination will give some indication of the response to enzyme treatment and may also help to identify non-compliant individuals.

Chemical measurement of faecal fat in carefully collected faecal samples is the traditional method of assessing fat absorption. Repeated measurements are extremely helpful in assessing the effectiveness of pancreatic enzyme treatment. Adequate facilities for processing samples do not exist in many laboratories and, for this reason, many centres do not have faecal fat assays available to them. Consequently most patients with cystic fibrosis in the United Kingdom do not have faecal fat estimated.

Many other alternative methods to chemical fat estimation have been described, but most have various shortcomings. Some involve the administration of isotopes, ^{131}I or ^{14}C , and measurement of the isotope in either faeces¹ or expired air.² Other methods involve blood sampling after a fat load and measurement of serum triglyceride.³ None of these procedures is particularly suitable in children. A simple, non-invasive screening test, which would give reliable qualitative measure of faecal fat loss, would be particularly useful in children.

We have compared the results obtained from chemical faecal fat assays with microscopic examination after fat staining⁴ and with the recently described 'steatocrit' method⁵ in 100 patients with cystic fibrosis.

Patients and methods

One hundred patients with proved cystic fibrosis (age range 6 months-27 years) were studied as outpatients. Each patient received a constant fat

diet for a seven day period; during this period they were also administered eight radio-opaque pellets three times per day, with each main meal.⁶ After five days equilibration, stools were collected for a further two days into strong polythene bags. The bags were x rayed and the pellets counted to assess the completeness of collections. The faecal samples were then homogenised with two volumes of water and the faecal fat determined chemically.⁷ For the purpose of comparison, faecal fat results are defined as: normal, <20 mmol/day; mild, 20-39 mmol/day; moderate, 40-59 mmol/day; or severe steatorrhoea, >60 mmol/day.

The homogenates were also examined after staining with Sudan III as follows, for neutral and split fats.

NEUTRAL FATS

One drop of faecal homogenate or a small pellet of faeces plus one drop of water was placed on a glass slide and one drop of 95% ethanol added and mixed with a coverslip. Two drops of Sudan III, saturated solution in 95% ethanol, were then applied and well mixed. The slide was then examined under low power ($\times 150$) for the presence of free triglycerides and soaps; these appear in various forms as wads, plaques, occasionally globular or almost crystalline, and generally stain a deep orange.

SPLIT FATS

Samples were applied to a glass slide as above and one drop of 36% acetic acid added and then well mixed using a coverslip. Two drops of Sudan III were then added and mixed in well. The slide was heated gently, almost to boiling, three times and then examined while warm for split fats. The free fatty acids appear as intensely red-orange stained globules with great variation in size.

In 19 samples the microscopic fat examination of a pellet of solid stool before homogenisation was compared with the result in the same sample after homogenisation (table).

The steatocrit method was carried out on 50 of the chemically assayed faecal fat samples. A standard haematocrit tube (75 mm Dade Co) was filled with faecal homogenate and spun in a Hawksley haematocrit centrifuge for 15 minutes. The tubes were removed and carefully examined. Usually a lower solid layer of faecal debris and liquid layer above was evident, and sometimes an upper fatty layer above this. The lower solid (S) and upper fatty (F) layers were measured

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Faecal fat microscopy compared in 19 stool samples before and after homogenisation

Sample No	Faecal fat (mmol/day)	Solid stool		Homogenate	
		Neutral fat	Split fat	Neutral fat	Split fat
1	111.6	+++	+++	+++	+++
2	25.0	++	+++	++	++
3	34.9	+++	++	++	++
4	45.8	++	++	++	++
5	13.0	+	+	+	+
6	130.9	+++	+++	+++	+++
7	15.8	+	+	+	+
8	62.3	++	++	++	++
9	84.5	+++	+++	++	+++
10	59.8	+++	+++	+++	+++
11	51.7	+++	+++	+++	+++
12	26.8	+	+	+	+
13	38.4	++	++	++	++
14	63.7	++	+++	++	+++
15	29.9	++	++	+	++
16	110.9	+++	+++	+++	+++
17	218.2	+++	+++	+++	+++
18	38.0	+	++	+	+
19	4.9	+	+	+	+

and the steatocrit expressed as a percentage using the formula:

$$S = \frac{F}{S+F} \times 100$$

Results

Microscopic examination was graded as negative where only traces of fat were seen, or +, ++, +++ for increasing quantities of fat staining, either as neutral or split fats. Neutral fat usually stained as clumps rather than as discrete globules as seen with split fat. A one + corresponded to 10 or more fatty globules of 10 µm diameter or greater. Two ++ corresponded to a significant excess of fat and this result was given when the sample showed material with 20–100 fatty clumps or globules in the range 10–50 µm in diameter. Three +++ indicated appreciable excess fat and was given where examination showed very large numbers (>100) of fatty clumps or globules, many of large diameter.

The microscopic results in the 19 samples where both solid stool and homogenised samples were compared are shown in the table. Overall, there was excellent agreement for split fat microscopy, whether a solid stool sample or a sample of the resulting homogenate was used. In only two samples (Nos 2 and 18) was a slight discrepancy seen. Good agreement was also seen when neutral fat was examined, only three samples showing a slight discrepancy (Nos 3, 9, and 15).

NEUTRAL FATS (FIG 1)

Of 100 patients, 80 had steatorrhoea and 11 of these were negative on microscopy, giving a sensitivity of 86% and a positive predictive value of 91%. Of the 20 patients without steatorrhoea seven were positive on microscopy, giving a specificity of 60% and a negative predictive value of 56%.

SPLIT FATS (FIG 2)

Of the 80 patients with steatorrhoea, 77 were positive on microscopy, giving a sensitivity of 96% and a positive predictive value of 90%. Nine of the 20 patients without steatorrhoea

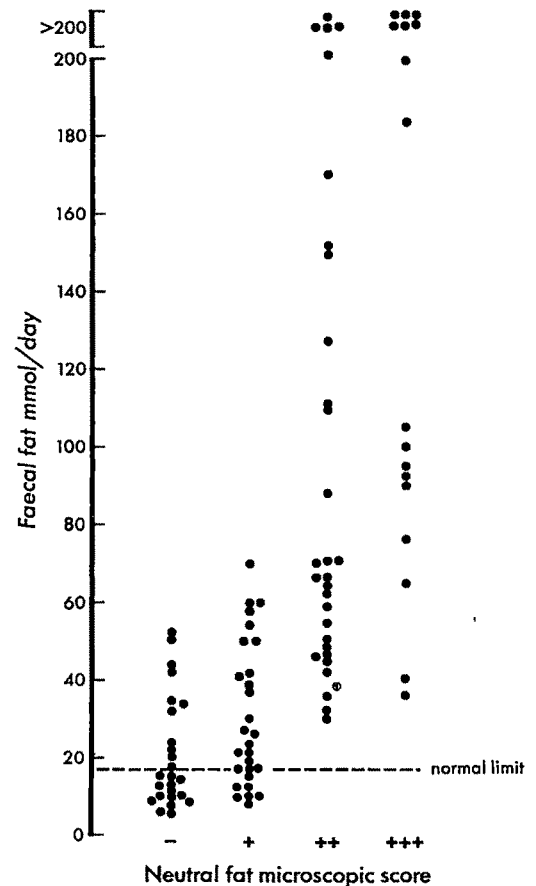


Figure 1 The results for faecal neutral fat as assessed by microscopy after fat staining in patients with cystic fibrosis and fat malabsorption of varying severity.

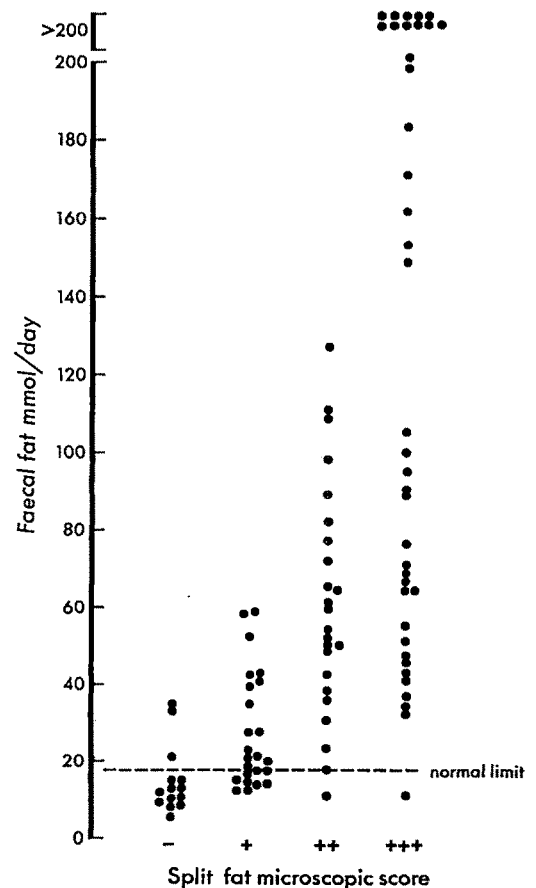


Figure 2 The results for faecal split fat as assessed by microscopy after fat staining in patients with cystic fibrosis and fat malabsorption of varying severity.

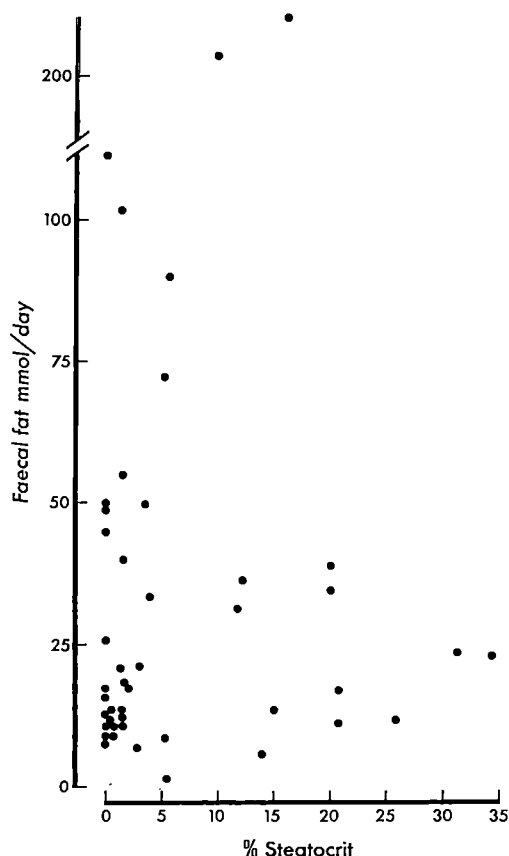


Figure 3 The association between faecal fat (mmol/day) and the steatocrit (%) in 45 patients with cystic fibrosis with varying severity of steatorrhoea.

were positive on microscopy, giving a specificity of 55% and a negative predictive value of 79%.

In our hands the steatocrit method proved unreliable and, in many samples, we failed to get a meaningful result. Frequently it was impossible to obtain a clear fat layer at the top of the haematocrit tubes and the fat appeared to be retained by the solid layer at the bottom of the haematocrit tube. In 45 samples where a steatocrit value was obtained, there was little association with either the chemical faecal fat result (fig 3) or the microscopic staining and, using this method, neither the exclusion of steatorrhoea or assessment of its severity was possible.

Discussion

Providing dietary intake is adequate, a major factor in determining the nutritional state of patients with cystic fibrosis is their ability to digest and absorb the food components of the diet. Fat malabsorption is common in these patients and the resultant steatorrhoea is often severe. The only reliable method of assessing the severity of steatorrhoea is a measure of faecal fat loss, and this is also required for assessing the effects of enzyme treatment.

Faecal fat assays are unpopular with patients and ward and laboratory staff, and some centres do not have the assay available. While the chemical faecal fat assay, when available, will remain the gold standard for assessing fat malabsorption, a simple and rapid, qualitative or semiquantitative assay would be extremely useful, particularly in those centres without the

necessary methodology, and where frequent changes in enzyme dose are made.

The initial description of the steatocrit method reported very encouraging results, and correlated well with chemical faecal fat assays.⁵ To our knowledge, only one other brief report has been published using this method, and the results were also satisfactory in excluding steatorrhoea.⁸ In our study we encountered considerable technical difficulties with this method even though, as far as we can determine, the method has been performed exactly as originally described. Some samples were analysed fresh without storage and again after storage, but storage time had no effect on the method. Various methods of homogenisation were attempted but, again, did not influence the results. The major technical difficulty was an inability to obtain clear separation of the fatty, aqueous, and solid layers after centrifugation. Frequently fat remained entrapped in the lower solid layer, demonstrated by Sudan III staining of the haematocrit tube contents. In the 45 samples where a result was obtained, there was no meaningful association between the steatocrit result and either the chemical faecal fat (fig 3) or the microscopic fat results. We have no explanation why our results are so different from the Italian workers', but in our hands this method would not serve as a screening test.

Stool microscopy has been reported by various authors previously, and the results have generally been encouraging. Drummey *et al* described the method as being simple, rapid and a valid method for screening for steatorrhoea,⁹ while Ghosh *et al* found the method useful in excluding steatorrhoea in children.⁴ More recently, Luk and Bin *et al* reported the method as both specific and sensitive.^{10 11} Indeed, a more recent report suggests that Sudan staining is specific for triglyceride and fatty acid and the method may be more specific than chemical faecal fat assay for assessing triglyceride and fatty acid losses.¹² The present results, particularly using split fat, showed a high sensitivity of 97% but specificity was only 46%. Of the 80 patients with steatorrhoea, only three were not detected by microscopy and all three had mild (20–40 mmol/day) steatorrhoea. The poor specificity of this technique will result in some patients without steatorrhoea being investigated further for non-existent steatorrhoea. There was some correlation between the microscopic grading and the severity of steatorrhoea; all patients with severe steatorrhoea (>60 mmol/day) were graded ++ or +++ by microscopy. Thus microscopic examination of faecal samples will detect the vast majority of patients with steatorrhoea and may give an indication of its severity.

It is suggested that information provided by regular faecal microscopy in patients with cystic fibrosis will detect those with severe steatorrhoea, which still occurs despite modern microsphere enzyme preparations. In those centres where faecal fat measurements are not available, monitoring of adequacy of pancreatic enzyme treatment by faecal microscopy will lead to better control of steatorrhoea and general nutrition.

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Optic nerve hypoplasia: associations and management

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Abstract

Since its first description optic nerve hypoplasia has been identified with increasing frequency, and a range of associated problems have been described. The major neurological and endocrine associations are well established, but those factors that predispose to the development of optic nerve hypoplasia remain unclear. To understand the aetiology of these problems better, and to formulate a management regime, we studied a consecutive series of 40 patients who were divided into three groups. Group 1 (n=24) had severe bilateral optic nerve hypoplasia; group 2 (n=10) had mild, bilateral optic nerve hypoplasia; and group 3 (n=6) had unilateral optic nerve hypoplasia. Previously described aetiological factors (for example, low maternal age or maternal alcohol or drug ingestion) were not present in any of the groups; this removes the need to screen a specific population. It is important that careful neurological and developmental assessments are carried out in children with optic nerve hypoplasia to identify potential disease. The role of imaging is discussed.

The diagnosis of optic nerve hypoplasia has been made with increasing frequency since its early descriptions,^{1 2} and it is no longer considered a rarity. A number of predisposing factors have been described, including maternal anticonvulsant ingestion,³ low maternal age,⁴ maternal alcohol or drug abuse,^{5 6} prenatal intracranial pathology,⁷ etc. In addition a wide range of neurological⁸ and endocrine⁹ associations have been recorded.

In view of this array of associations it is difficult to identify a practical and appropriate management regime for each child with optic nerve hypoplasia. In particular, certain clinically important questions have not been directly addressed. Do only those children with severe optic nerve hypoplasia have neurological and endocrine problems? Do all children require some form of central nervous system imaging? Do positive results from such imaging inevitably presage a clinical deficit?

In order to answer these questions better, we have reviewed a series of 40 children seen at our hospital with optic nerve hypoplasia, and attempted to evaluate the frequency of some recognised associations. We discuss their significance, current concepts of pathogenesis, and formulate a guide to the management of these children.

Patients and methods

A diagnosis of optic nerve hypoplasia was made or confirmed by one of us (HEW) based on the appearance of a combination of features, the most important of which were (a) a small optic nerve head, (b) a second pigmented ring around the disc, and (c) tortuosity or abnormal origin of the vessels arising from the disc.¹⁰ Rarely were all features present in any one eye. A detailed history was obtained from the mother in every case, specifically including the obstetric history, a history of smoking, alcohol consumption, or drug ingestion during pregnancy, and a history of problems in the neonatal period. The child's development and growth pattern were recorded and in all bilateral cases, and three unilateral, examination by a paediatric neurologist (SHG) was performed. In addition, most children had computed tomography performed, and, where it was considered appropriate, their endocrine state was investigated and any deficiency treated. Serial visual acuity measurements were taken using tests appropriate for age, and included preferred looking acuities in very young or retarded children.

Results

Of the 40 children included in this study, 34 were bilaterally affected, with 24 considered to have a severe degree of optic nerve hypoplasia, and 10 had relatively minor changes. All children who were severely affected showed pallor of the residual disc tissue. Only six children with strictly unilateral involvement were identified, though one child with bilateral optic nerve hypoplasia had appreciable asymmetry of affect. The difference in number between these groups may well reflect our status as a tertiary referral centre rather than the true distribution of the disorder. The three groups of children are considered separately, and their important clinical features are summarised in tables 1, 2, and 3.

The children with severe, bilateral optic nerve hypoplasia (group 1, n=24) all presented because of poor vision and roving eye movements. Vision varied between 6/36 and no perception of light with most children showing perception of light only. Of the 24 children, 15 had an identifiable neurological deficit, ranging from global retardation to focal pathology such as epilepsy or hemiparesis. Computed tomography was performed on 20 of this group (of the remaining four, three failed to attend for radiographic examination and one was beyond puberty at the time of presentation with no abnormal neurological signs) and 15 were

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Table 1 Group 1: children with bilateral, severe optic nerve hypoplasia (n=24)

Case No	Visual acuity	Neurological disorders	Endocrinological disorders	Findings on computed tomography	Comments
1	1/60	Ataxia	Normal	Normal	Jaundice
2	PL	Normal	Normal	Not done	
3	PL	Normal	Normal	Normal	
4	PL	Epilepsy	Panhypopituitarism	Agensis corpus collosum	
5	PL/HM	Normal	Normal	Cortical atrophy	
6	PL	Retarded	Normal	Cortical atrophy	
7	PL	Retarded	Normal	Cortical and cerebellar atrophy	
8	PL	Normal	Normal	Not done	
9	2/60	Normal	Normal	Normal	
10	3/60	Normal	Normal	Cortical and cerebellar atrophy	X linked albino
11	PL	Retarded	Normal	Normal	Fetal alcohol syndrome
12	3/60, 6/36	Retarded	Reduced somatotrophin	Absence septum pellucidum	
13	6/36	Normal	Reduced somatotrophin	Absence septum pellucidum	Neonatal hypoglycaemia
14	PL	Hemiparesis	Normal	Porencephaly	
15	NPL	Spasticity/retarded	Normal	Porencephaly/agenesis corpus collosum	
16	PL	Spasticity/retarded	Normal	Porencephaly	
17	PL	Normal	Normal	Agensis corpus collosum	
18	HM	Retarded	Normal	Porencephaly	
19	4/60	Spasticity	Normal	Normal	
20	PL	Retarded	Hypopituitarism	Porencephaly	
21	PL	Fits/retarded	Normal	Not done	
22	PL	Epilepsy	Normal	Porencephaly	
23	2/60	Normal	Reduced somatotrophin	Not done	
24	PL	Retarded	Normal	Cortical atrophy	

PL, perception of light; NPL, no perception of light; HM, hand movements.

Table 2 Group 2: children with bilateral, mild optic nerve hypoplasia (n=10)

Case No	Visual acuity	Neurological disorders	Endocrinological disorders	Findings on computed tomography	Comments
25	PL/HM	Retarded	Normal	Porencephaly	
26	6/9, 6/6	Hemiparesis	Normal	Dilated lateral ventricle	
27	6/12	Normal	Normal	Enlarged basal cistern	
28	6/12	Normal	Normal	Normal	Fetal alcohol syndrome
29	6/18	Normal	Normal	Dilated ventricles	
30	6/6, 6/18	Normal	Normal	Normal	
31	6/12	Retarded	Normal	Normal	
32	6/12, 6/6	Retarded	Normal	Dilated ventricles	
33	6/9	Normal	Reduced somatotrophin	Absence septum pellucidum	
34	6/9	Normal	Normal	Not done	

PL, perception of light; HM, hand movements.

Table 3 Group 3: children with unilateral optic nerve hypoplasia (n=6)

Case No	Visual acuity	Neurological disorders	Endocrinological disorders	Findings on computed tomography	Comments
35	6/9	Hemiparesis	Normal	Porencephaly	
36	CF	Retarded	Normal	Normal	
37	6/12	Retarded	Normal	Normal	
38	6/60	Normal	Normal	Normal	
39	6/12	Normal	Normal	Not done	
40	6/9	Normal	Normal	Not done	

CF, counting fingers.

abnormal. The range of abnormalities found on computed tomography is shown in table 1, but it should be noted that three of the five children with midline abnormalities had endocrine deficiency, and eight of the 10 children with non-midline pathology had a neurological deficit. Conversely three of the five children with entirely normal scans also had clinical evidence of a neurological deficit.

The mean maternal age in the children with severe, bilateral optic nerve hypoplasia was 26.8 years, the mean paternal age 27.6 years, and only one couple were below 20 at the time of their child's birth (two mothers and two fathers were over 30). No mother took anticonvulsants, two took antiemetics in the first trimester, and one regularly took antihistamines. One mother

was alcoholic and her daughter showed the other dysmorphic features of the fetal alcohol syndrome.¹¹ Only three mothers smoked during pregnancy, and four mothers suffered threatened abortions during the first trimester. One child in this group had severe neonatal hypoglycaemia.

A similar analysis of those children with less severe bilateral optic nerve hypoplasia (group 2, n=10) showed that six children had abnormal computed tomograms. One child with midline developmental abnormalities was deficient in growth hormone, and three of the children with other abnormalities found on computed tomography had neurological damage. In this group the mean maternal age was 27.2 with no mothers under 20 or over 32; the mean paternal

age was 31.6. One mother in this group was alcoholic, and one mother was addicted to a proprietary cough medicine. There was no history of smoking or other drug ingestion among the remaining mothers.

In the children with unilateral optic nerve hypoplasia (group 3, $n=6$), three children had serious neurological abnormalities, though in only one was this predicted by an abnormal computed tomogram. In these children the optic nerve hypoplasia was a chance finding in two, and in the remainder was found after presentation with strabismus or amblyopia.

Discussion

The different entities reported to be associated with optic nerve hypoplasia appear to be legion, and only by reviewing large groups of patients is it possible to avoid false impressions gained as a result of biased ascertainment. This series, because of the nature of our hospital, is certainly biased but considered along with other large series¹²⁻¹³ allows us to evaluate critically some of the associations previously described.

After the original report in 1978³ no children have been recorded in whom maternal anti-convulsant ingestion has been a predisposing feature. Furthermore, review of an epilepsy service showed no affected mothers having visually handicapped children (J A Finnegan, personal communication). While this does not rule out mild optic nerve hypoplasia, it must now be considered that this described association is probably an unusual artefact of recruitment. Though phenytoin in particular is known to be teratogenic,¹⁴ the explanation of the 1978 findings remains obscure. Similarly, though the largest series published did not address the question of maternal or paternal age,¹² there is no evidence in this group of parents to support the concept of low maternal age as a predisposing factor. The other reported links with maternal alcoholism⁵ and maternal drug ingestion⁶ are supported so far as alcoholism is concerned, but it is impossible to draw any conclusions about an association with the ingestion of hallucinogenic drugs. A possible connection with severe neonatal hypoglycaemia has been described,¹⁵ and one of our children required intravenous glucose in the first three days of life. Though most children with optic nerve hypoplasia give no such history it would certainly be wise to ensure a detailed ophthalmic examination on any neonate with severe hypoglycaemia. There appears, however, to be a large pool of affected children in whom the aetiological agent has not been identified. The pathogenesis of optic nerve hypoplasia remains uncertain, but it is likely that the documented reduction in numbers of ganglion cells in the retina of affected eyes is a secondary rather than a primary event as the other cells derived from the same stem as the ganglion cells are not reduced in number.¹⁶ Retrograde degeneration of developing axons, which is an established feature of normal optic nerve development,¹⁷ may well be excessive in these children. Presumably some insult leads to this excessive retrograde degeneration, and experimental

evidence has shown that, in the case of alcohol at least, the insult must be delivered in the early weeks of pregnancy.¹⁸ In animal models the timing of the alcohol infusion to cause optic nerve hypoplasia is critical, and the same work showed that a similar dose in different individuals was capable of leading to a variable severity of affect. The mechanism of alcohol toxicity may well be enhanced degeneration, again supporting this concept of the pathogenesis of human optic nerve hypoplasia.

The incidence of porencephaly in children with optic nerve hypoplasia is worthy of comment. There have been several isolated reports of such an association, including histopathological examination of the eyes and brain,¹⁹ but generally greater attention has focused on midline pathology. However, analysis of the 93 patients of Skarí and Hoyt and the current series shows porencephaly to be the more common finding on computed tomography.¹² Porencephaly commonly results from a vascular insult to the developing nervous system,²⁰ and Myers found both porencephaly and reduced ganglion cells in the offspring of a monkey suffering partial placental abruption in early pregnancy.²¹ The possibility that some first trimester obstetric event might trigger the central nervous system and optic nerve problems is appealing, but among the total group of 40 patients, only five mothers suffered an identifiable event in the first 10 weeks of pregnancy. This figure would not be remarkable in a group of 40 pregnancies so once again the association must remain speculative.

In the absence of any other recognisable cause, could disease in the central nervous system obstruct the development of normal synaptic connections, or alternatively prevent proper cortical induction of the developing visual pathways? Taylor has argued that the presence of a space occupying lesion (including a porencephalic cyst) may act as a barrier to normal synaptic development, and felt that this mechanism explained his observation of an incidence of associated developmental tumours of the anterior visual pathways.⁷ No child in this series showed evidence of tumour formation, indeed it is an extreme rarity to identify tumour formation in a child where the diagnosis of optic nerve hypoplasia has first been established (as opposed to identifying optic nerve hypoplasia in a child with a known tumour). None the less, it does seem likely that the pathogenesis of optic nerve hypoplasia involves a block to normal visual pathway development, either by some intracranial pathology, or by a vascular insult that simultaneously leads to intracranial pathology.

Like other authors we have identified a high incidence of neurological and endocrine associations. We have not undertaken the major endocrinological assessment previously reported,¹² four of 24 severely affected children and one of 10 mildly affected, however, showed clinical and biochemical evidence of major hormone deficiency. The incidence of neurological associations is even more striking (62.5% of group 1 and 40% in group 2). It is disappointing to find, however, that while both the severity of optic

nerve hypoplasia and findings on computed tomography are suggestive of neurological problems, neither predicts absolutely. This raises the question of how these children may best be managed at a clinical level. The significant incidence of neurological deficit in children with normal scans (six of the total group of 40), and conversely the incidence of children with abnormal scans but no identifiable neurological problems (five of 40) suggests that while scanning provides information on the likelihood of problems, it is not reliably predictive in any one child. If the risk of developmental visual pathway tumours can be confirmed, then scanning (or ultrasonography in the very young) would be mandatory. If this association is not confirmed then it is our belief that these children can be well managed by careful clinical assessment and prolonged monitoring of growth and development, without recourse to expensive investigations.

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Carbohydrate deficient serum transferrin in a new systemic hereditary syndrome

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Abstract

Four patients with a new, inherited, complex developmental deficiency syndrome were studied. The syndrome affects the central and peripheral nervous system, and also the retina, liver, bone, adipose tissue, and genital organs. Abnormalities of glycoproteins, glycopeptide hormones, and lipids have been found in serum from these patients, the most pronounced being increased cathodal forms of transferrin. Isoforms of serum transferrin were therefore analysed qualitatively and quantitatively by isoelectric focusing and isocratic anion exchange chromatography, and the carbohydrate composition was determined in transferrin isolated by immune affinity chromatography. All the patients had about tenfold raised serum concentrations of isotransferrins with higher isoelectric points than normal. Similar findings, though less pronounced, were made in all the fathers and in one of the mothers. Half the transferrin in the patients was constantly present in two principal abnormal cathodal forms in approximately equal amounts. Carbohydrate determinations in purified transferrin showed quantitatively similar deficiencies of sialic acid, galactose, and N-acetylglucosamine, the mannose content being normal. The results suggest that either two or all of the normally four terminal trisaccharides in transferrin may be missing. A defect in the synthesis or catabolism, or both, of this trisaccharide, which is common to many secretory glycoconjugates, is likely. Apart from providing a quantitative diagnostic method, the present findings may serve as a basis for further studies of the metabolic deficiency in this syndrome.

plasmic reticulum and Golgi apparatus, and lipid and membrane like inclusions in the lysosomes of hepatocytes.²

A number of abnormalities of serum glycoproteins, lipids, hormones, and enzymes have been found in these patients—for example, low concentrations of albumin, haptoglobin, apoprotein B, thyroxine binding globulin, transcortin, and cholesterol in the serum, and fluctuating concentrations of prolactin, growth hormone, and follicle stimulating hormone.^{1,2} Some lysosomal enzyme activities in serum are raised, (arylsulphatase A, beta-galactosidase and N-acetylglucosaminidase), and others are normal (sialidase and alpha-mannosidase).² The microheterogeneity of transferrin from serum and cerebrospinal fluid was abnormal in all the patients, suggesting a deficiency in the negatively charged carbohydrate sialic acid.¹ A similar abnormality was also found in other serum glycoproteins, but to a lesser extent.²

Studies of the carbohydrate content of total serum glycoproteins indicated that the carbohydrate deficiency was complex and included a reduction of about 40% not only of sialic acid, but also of galactose and N-acetylglucosamine in the patients and to a lesser degree in their fathers as well.^{1,2} The carbohydrate content of total serum glycoproteins is, however, affected by the concentrations of the various glycoproteins, which also differ in their individual carbohydrate content and composition. In order to obtain more detailed information on this carbohydrate deficiency in a single quantitatively important glycoprotein, serum transferrin isoforms were studied qualitatively and quantitatively, and the carbohydrate content was determined in the isolated glycoprotein.

Subjects and methods

For analysis of carbohydrate concentrations in transferrin, serum was prepared from venous blood from the four female patients aged 2.5–12 years,^{1,2} and from four age matched controls. The patients, including monozygous twins, came from three unrelated families (table 1). For qualitative and quantitative analyses of isoforms of serum transferrin, samples were collected from six control children aged 2–14 years, from two clinically unaffected siblings aged 3.5–4 years, and from the three clinically healthy fathers and mothers. There was no history of alcohol abuse in the parents, and they had agreed not to use any alcohol for the two weeks preceding sampling.³

Serum samples were immediately frozen and

A new hereditary disorder has recently been identified in four girls with severe neurological symptoms associated with complex biochemical abnormalities.^{1,2} The neurological syndrome includes psychomotor retardation, pronounced cerebellar hypoplasia with corresponding cerebellar dysfunction; alternating internal strabismus, and peripheral sensorimotor neuropathy.^{1,2} Convulsions and stroke like episodes have occurred in some patients.² Other organs are variably affected, including retinitis pigmentosa, skeletal abnormalities, lipodystrophy and fat accumulations on the buttocks, hypertrophy of the labia majora, and retracted nipples.^{1,2} In all four patients there was variable hepatomegaly with distension of the endo-

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Table 1 Summary of principal clinical symptoms shown by the patients

Growth mostly at or below the third centile
Psychomotor retardation without regression
Alternating internal strabismus
Hypotonia, trunk ataxia, hyporeflexia
Localised fat accumulations, lipodystrophy, obesity
Prominent thorax, scoliosis
Variable hepatomegaly
Variable retinitis pigmentosa
Unexplained fits with coma, convulsions, and hemiplegia

stored at -80°C until analysed. The samples were transported without thawing in dry ice from Belgium to Sweden within 24 hours.

ISOELECTRIC FOCUSING

A 40 μl sample of whole serum diluted 1:75 in distilled water was analysed from each subject in thin layer polyacrylamide gel in a pH gradient ranging from 2.2 to 11⁴ and stained by silver staining.⁵ Transferrin components were identified by subsequent immunofixation of serum samples containing a constant amount of transferrin (0.5 μg) using antibodies against human serum transferrin (DAKO).⁶ Samples containing 25 μg of iron saturated purified transferrin from each subject were examined and stained with Coomassie brilliant blue. Densitometry was then carried out and the relative amount of each component was calculated as a percentage of the total.⁷ Genetic typing of serum transferrin was carried out in the patients after neuraminidase treatment of serum, isoelectric focusing, and immunofixation using a sample with a known phenotype of C 1-2 as reference.⁸ Total transferrin concentration in the serum and in the samples with purified transferrin were determined by single radial immunodiffusion on NOR-Partigen plates (Behring).

DETERMINATION OF CARBOHYDRATE DEFICIENT TRANSFERRIN (CDT) IN SERUM

After iron saturation and dilution, duplicate samples of 100 μl of serum were subjected to isocratic microanion exchange chromatography at pH 5.65 after which a transferrin radio-immune assay of the eluate was carried out as previously described.³ This method, initially developed for diagnosing alcohol abuse, measures the concentration of cathodal isotransferrins in serum (isoelectric point ≥ 5.7) while the normal main components (isoelectric point < 5.7) are retained by the anion exchanger.³ Except when rare genetic D variants of transferrin are present,⁹ increased concentrations of carbohydrate deficient transferrin ($> 74 \text{ mg/l}$) indicate a reduction in the content of the charged carbohydrate sialic acid in transferrin.³ Variations in the content of neutral carbohydrate in transferrin (galactose, N-acetylglucosamine, and mannose) can probably not be detected by this method.¹⁰ The specificity of this assay for detecting alcohol abuse is 99% in large clinical studies in adults.^{3 11 12}

PURIFICATION AND CARBOHYDRATE

DETERMINATIONS OF SERUM TRANSFERRIN

Samples of 2.5 ml of serum from patients and

controls were diluted 1:1 in 0.05 M sodium orthophosphate and 0.02 M sodium citrate at pH 7.2, and applied to 1.2 ml columns of antitransferrin-Sepharose 4B. Chromatography was carried out as previously described.^{13 14} Two columns were used for each individual. The eluted transferrin from each subject was pooled, neutralised, dialysed, and concentrated to a final transferrin concentration of 1.56–5.34 g/l as determined by single radial immunodiffusion.¹⁴ Aliquots were saturated with iron and subjected to isoelectric focusing while the remainder of the concentrated eluates was used for carbohydrate analyses.¹⁴

The amounts of sialic acid, galactose, N-acetylglucosamine, and mannose were determined after acid hydrolysis by colorimetric^{15 16} or enzymatic¹⁷ methods previously described,¹⁴ with the exception that the galactose content was analysed after hydrolysis in 0.5 M sulphuric acid at 100°C for four hours, which had been found to improve reproducibility (H Stibler, unpublished observations). All samples were analysed for the same carbohydrate simultaneously on the same day and at least two specimens were examined. The variation of these methods (SD), varied between 0.07 and 4.7 nmol.¹⁴

Results

In the type of pH gradient used for isoelectric focusing, normal, iron saturated serum transferrin separates into six components within the pH range 5.2–5.7.⁴ The normal main component has an isoelectric point of 5.4 and corresponds to transferrin containing four sialic acid residues in its two carbohydrate chains (tetrasialotransferrin).^{4 10 14 18} Anodal and cathodal isotransferrins are normally minor bands: higher glycosylated forms with isoelectric points of 5.2 and 5.3, and trisialotransferrin and disialotransferrin with isoelectric points to 5.6 and 5.7, respectively.^{4 10 14 18} In all the patients there was a pronounced abnormality of the microheterogeneity of transferrin in native serum as well as in transferrin purified by affinity chromatography (figs 1 and 2). There was a pronounced increase (see below) of components with isoelectric points of 5.7 and 5.9 (disialotransferrin and asialotransferrin). Only a minor band at isoelectric point 5.8 (monosialotransferrin) was present, while components corresponding to trisialotransferrin, tetrasialotransferrin, and pentasialotransferrin (isoelectric points 5.6, 5.4, and 5.3, respectively) were less marked than normal. Moderate increases of disialotransferrin and asialotransferrin were observed in serum from all the fathers (fig 1). Neuraminidase treatment completely abolished the abnormal transferrin heterogeneity, and transferrin phenotypes were the common C1 in three patients, and C1-2 in one patient.

Quantitative determination of carbohydrate deficient transferrin (isoelectric point > 5.65) showed approximately a tenfold rise in cathodal isotransferrins in all the patients compared with normal values,^{3 9 12} The carbohydrate deficient transferrin values were on average twice the normal in all three fathers, and slightly higher than normal in one of the mothers (86 mg/l).

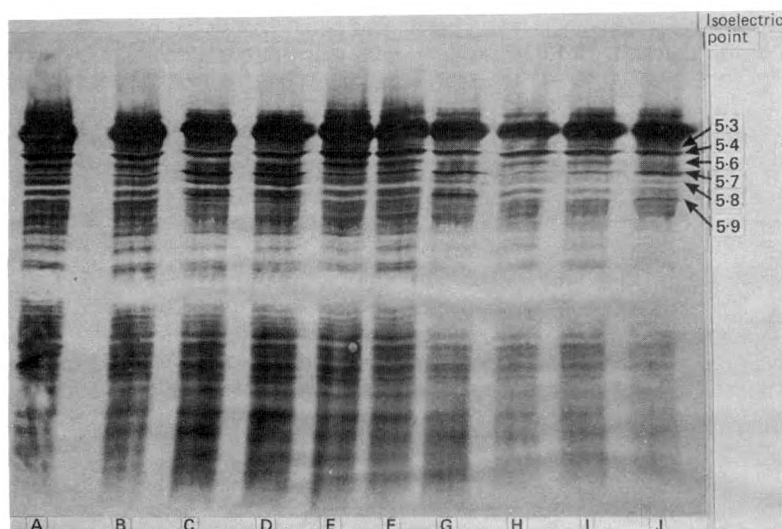
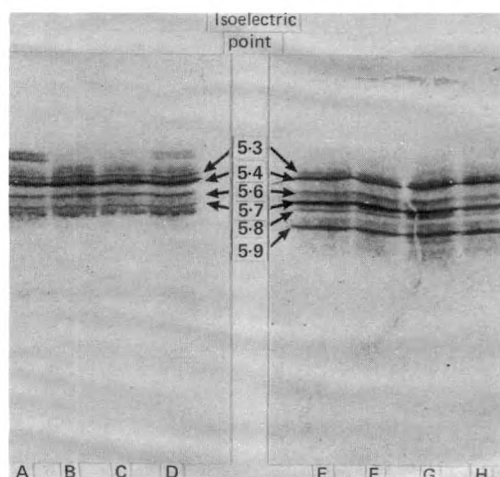


Figure 1 Isoelectric focusing of native serum proteins with silver staining within the pH range 2.2–11. The isoelectric points of transferrin are indicated at the right. A=mother of C and D. B=father of C and D. C and D=patients. E=mother of G. F=father of G. G=patient. H=mother of J. I=father of J. J=patient. Note the increase of disialotransferrin and asialotransferrin (isoelectric points 5.7 and 5.9) and the low amount of trisialotransferrin and monosialotransferrin (isoelectric point 5.6 and 5.8) in the patients. Note also the slight increase of disialotransferrin in the fathers. The transferrin pattern seems normal in the mothers.

Figure 2 Isoelectric focusing (as in fig 1) of 25 µg of serum transferrin isolated by affinity chromatography and stained with Coomassie brilliant blue. The isoelectric points indicate transferrin components. A to D=transferrin from controls, E to H=transferrin from the four patients. Note the preserved pronounced abnormality in transferrin from the patients. The most anodal band in some samples is contaminating albumin. The poorly focused material just cathodal to isoelectric point 5.7 is lipid.



The other two mothers and the siblings had normal carbohydrate deficient transferrin concentrations (table 2). For the sake of comparison, carbohydrate deficient transferrin values from alcoholic patients are included in table 2. Total transferrin concentration in serum was reduced (1.40 and 1.56 g/l) in two of the patients, but normal in the other two cases (2.05 and 2.94 g/l) (normal range 2.02–3.90 g/l).

Table 2 Concentrations of carbohydrate deficient transferrin in serum of patients, family members, and controls

Subjects	Mean (SD) carbohydrate deficient transferrin concentration (mg/l)
Patients (n=4)	591 (77)
Siblings (n=2)	63 (2)
Child controls (n=6)	62 (18)
Fathers (n=3)	125 (50)
Mothers (n=3)	64 (15)
Healthy adult controls (n=155) ^{3, 26}	53 (11)
Alcoholic patients (n=100) ^{3, 26}	133 (57)

Isoelectric focusing of immune affinity purified transferrin showed a preserved transferrin pattern and contamination with only traces of albumin (isoelectric point 4.8–4.9) and lipid (isoelectric point >5.7) (fig 2), as has been found before with this technique.¹⁴ As these contaminants contain no carbohydrate, they were not considered to affect the carbohydrate analyses.

In the patients, the percentage (SD) amounts of isotransferrins were 29 (4)% for the component with an isoelectric point of 5.7 (normal 3.7 (1.5)%⁷), and 24 (3)% for the one with an isoelectric point of 5.9 (normal 0%). Normal isoforms (isoelectric point 5.2–5.6) constituted 47 (3)% of the total amount. The carbohydrate values in control transferrin corresponded closely to those accepted for normal whole transferrin, and to values obtained by the same methods in adults (table 3).^{10, 14} Compared with healthy adults¹⁴ the values in child controls tended to be somewhat higher, especially of N-acetylglucosamine (+13%), which might either be analytical or indicate a slightly higher degree of transferrin glycosylation in children. In all the patients, the total contents of sialic acid, galactose, and N-acetylglucosamine in transferrin were much lower than in the control children. The average reduction was 31 (2)% for all three carbohydrates. The mannose content, on the other hand, was almost identical in the two groups (table 3). Together, carbohydrate deficient isotransferrins (isoelectric point 5.7–5.9) constituted 53 (2)% of the isolated

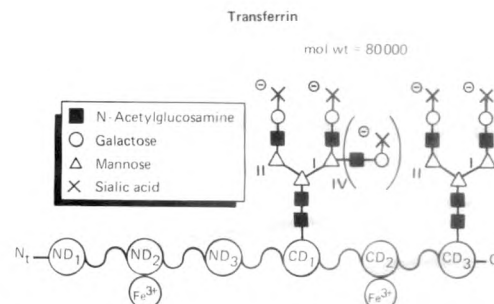


Figure 3 Oligosaccharide units of the main forms of normal transferrin. The trisaccharide in parentheses is normally present in only some of the molecules.¹⁰ The arrows indicate the sites of action of I=N-acetylglucosaminyltransferase I, which is essential for the action of II=N-acetylglucosaminyltransferase II and IV=N-acetylglucosaminyltransferase IV.²⁵

Table 3 Carbohydrate concentrations in purified whole serum transferrin from patients and controls

Carbohydrate	Patients	Controls
Sialic acid:		
Transferrin (µmol/g)	37.40 (2.07)	54.59 (2.27)
Transferrin (mol/mol)	2.8 (0.2)	4.2 (0.2)
Galactose:		
Transferrin (µmol/g)	38.73 (2.58)	54.71 (1.38)
Transferrin (mol/mol)	3.0 (0.2)	4.2 (0.1)
N-acetylglucosamine:		
Transferrin (µmol/g)	83.38 (4.36)	118.33 (5.06)
Transferrin (mol/mol)	6.4 (0.3)	9.1 (0.4)
Mannose:		
Transferrin (µmol/g)	76.05 (1.82)	78.85 (5.43)
Transferrin (mol/mol)	5.9 (0.1)	6.1 (0.4)

The molar ratios were calculated from a molecular weight of 77 000 for transferrin.

glycoprotein. The average reduction of the three saccharides may therefore amount to 66% in the abnormal fractions. As these mainly consisted of disialotransferrin (29%) and asialotransferrin (24%), and the three carbohydrates were reduced to the same extent, it may be suggested that the disialotransferrin component lacks two, and the asialotransferrin four, sialic acid, galactose, and N-acetylglucosamine residues peripheral to mannose (fig 3). Based on the relative amounts of normal and abnormal isotransferrins, this type of proposed carbohydrate defect would result in expected total carbohydrate contents of 2.6 for sialic acid and galactose, 6.9 for N-acetylglucosamine, and 6.1 for mannose (in mol/mol of transferrin), which are close to the total values obtained in the patients (table 3).

Discussion

The extreme alteration of transferrin microheterogeneity on isoelectric focusing, with more than half of this glycoprotein being abnormal in our patients, seems to be almost specific for this disease. An abnormality of this kind has also been described recently in seven Swedish children (four girls and three boys from four families) with a constellation of complex clinical symptoms similar to those in our cases.¹⁹ Based on the transferrin pattern on isoelectric focusing, these authors called the disease 'disialotransferrin developmental deficiency syndrome'.¹⁹ From their first figure it is, however, clear that both the disialotransferrin and asialotransferrin components were greatly increased in serum as in our patients. The clinical picture, together with the most unusual appearance of the transferrin, suggests that these patients suffer from the same or a closely related metabolic disorder. In several thousands of serum samples examined by isoelectric focusing by us and others^{19 20} a cathodal distribution of transferrin of this type, though less pronounced, has only been found in alcohol abusers. The same result has been obtained with the more rapid and simple quantitative carbohydrate deficient transferrin assay.^{3 9 11 12 21} Slightly increased carbohydrate deficient transferrin concentrations may occur in some patients with primary biliary cirrhosis, and in patients with rare genetic D-variants of transferrin.^{9 11 12} Carbohydrate deficient transferrin concentrations of the magnitude of those in the present cases, however, have only occasionally been found in alcoholics. With these exceptions in mind, the carbohydrate deficient transferrin assay seems to be highly specific for this syndrome.

The results of carbohydrate analyses in total serum glycoproteins^{1 2}, and now specifically in isolated transferrin, clearly show that the carbohydrate deficiency includes not only the charged sialic acid but also the neutral galactose and N-acetylglucosamine to almost exactly the same extent, which together constitute the terminal trisaccharides in transferrin (fig 3) and in many other secretory glycoproteins.²² The normal mannose content and the degree of reduction of N-acetylglucosamine suggest that

the oligosaccharide core is probably intact. The carbohydrate defect previously shown in total serum glycoproteins^{1 2} cannot be quantitatively explained by this abnormality in transferrin alone. Other serum glycoproteins can therefore be expected to be similarly affected, and this supposition is also indirectly supported by preliminary isoelectric focusing analyses.² One of the reasons why this change is more readily observed in transferrin may be its relative independence of the carbohydrate units for secretion and survival in circulation in contrast to many other serum glycoproteins.^{23 24}

The fact that the transferrin abnormality consists of increases of disialotransferrin and asialotransferrin, and only to a small extent of monosialotransferrin together with the reduced trisialocomponent, argues against a simple catabolic effect of glycosidases. Such an action would be expected to cause a successive or random increase in cathodal isotransferrin,^{4 18} provided that the recognition and elimination of transferrin with two or four defective oligosaccharide antennas is not selectively impaired.²³ The normal sialidase activity and normal concentrations of free sialic acid, galactose, and N-acetylglucosamine in serum are also evidence against a glycolytic mechanism.²

In view of the morphological pathology of the endoplasmic reticulum and Golgi apparatus, a synthesis defect has to be considered.² After en bloc incorporation of the core oligosaccharide in the rough endoplasmic reticulum, followed by mannose trimming, the carbohydrates of the terminal trisaccharides in serum glycoproteins are successively added in the Golgi complex.²⁵ In the case of transferrin at least five glycosyltransferases are needed for completion of the chain.²⁵ Considering the transferrin pattern and its carbohydrate contents in the patients, a partial deficiency of N-acetylglucosaminyltransferase I or II can be hypothesised (fig 3). Preliminary results have indicated a 40% reduction of non-specified N-acetylglucosaminyltransferase but also of sialyltransferase activity in serum.² To elucidate the basic defect, studies of the intracellular enzymes with specific isoenzyme analyses are in progress. It may be of interest that in alcoholic patients with a carbohydrate deficiency in transferrin similar to that shown by the patients with this syndrome,¹⁴ several glycosyltransferases have low activities, apparently as a result of an inhibitory action of acetaldehyde,²⁶ which also causes morphological changes of the Golgi apparatus.²⁷ The essential similarity in symptoms, particularly those of the nervous system, between this inherited syndrome and the acquired complications of chronic alcoholism in adults is notable. These two conditions may therefore offer ways to gain greater insight into the role of the carbohydrate moiety in secretory glycoproteins for the development and maintenance of the human nervous system.

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Fenfluramine in Prader-Willi syndrome: a double blind, placebo controlled trial

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Abstract

A double blind trial was conducted to determine the effect of fenfluramine on the weight and behaviour of patients with the Prader-Willi syndrome. Fifteen subjects, aged 5.5 to 27 years, received the placebo and the active drug, each for a period of six weeks. The dose of fenfluramine varied according to the age of the patient. Treatment with fenfluramine was associated with significant weight loss, improvement in food related behaviour, and a decrease in aggressive behaviour directed towards others. Skin picking and other self mutilation were unaffected by the drug. None of the subjects suffered from any side effects while taking the drug.

These findings suggest that short term treatment with fenfluramine may have a role in the management of some patients with Prader-Willi syndrome. It could be used during periods when exposure to large amounts of food cannot be avoided and aggressive behaviour is particularly difficult to contain. It may also be useful in those whose lives are threatened by the complications of obesity.

Prader-Willi syndrome is a congenital disorder that was first described in 1956.¹ It has a prevalence estimated at one in 10 000,² and is usually sporadic.³ The condition is characterised by infantile hypotonia, hypogonadism, and facial dysmorphism. The characteristic hyperphagia, and abnormal behaviour and intellectual functioning, usually do not become evident until after 2 years of age. The hyperphagia associated with Prader-Willi syndrome is severe and chronic, and is responsible for the early mortality of people with the condition. Behavioural difficulties are a prominent feature of the disorder during adolescence and adulthood.⁴ These behaviour difficulties include aggressive outbursts and picking at minor skin lesions, such as insect bites. The hyperphagia, together with the behavioural difficulties, make Prader-Willi syndrome one of the most serious and pervasive conditions with respect to its impact on the family unit.^{5 6}

The mainstays of the treatment of Prader-Willi syndrome are control of the environment, particularly in relation to the availability of food, and the implementation of behaviour management techniques.⁷ These methods are helpful, but have not proved completely successful, and the prognosis once adulthood is reached remains poor.⁸ This justifies a search for other forms of treatment that may be used in conjunction with these techniques.

Reviews of Prader-Willi syndrome have stated that anorexic drugs have no place in its management.⁷⁻¹⁰ Nevertheless, none of these reviews refers to a controlled trial of an anorexic drug, and we were unable to find any report of such a trial. Naloxone, an opiate antagonist, was given by subcutaneous injection to three patients with Prader-Willi syndrome in a double blind, placebo controlled trial, but with equivocal results.¹¹

Fenfluramine (Ponderax) is an anorexic drug that has been in clinical use for over two decades and has few side effects.¹² We present the results of a double blind, placebo controlled trial to assess the effect of short term fenfluramine on the weight and behaviour of children and young adults with Prader-Willi syndrome.

Patients and methods

The patients taking part in this study were randomly selected from the 38 attending our clinic, who were over the age of 5 years, and conformed to the accepted diagnostic criteria of Prader-Willi syndrome. Informed consent was obtained from the parents and from the patients if they were old enough to give it.

They were randomly assigned into one of two groups. During the period of the trial, caregivers were instructed to continue with the same diet, exercise, and behaviour management techniques that were being followed before the trial started.

There was an initial two week period during which observations were made to obtain baseline data. Thereafter one group received the active drug for a six week period, followed by the placebo for a six week period. At the same time the other group received the placebo for the first six weeks and the active drug for the second six weeks.

Placebo and active drug were prepared in identical opaque capsules by a pharmacist who took no further part in the trial. The placebo capsules contained lactose. No one else knew which capsules contained the active drug and which contained the placebo until after data collection was complete.

The dose of fenfluramine in the capsule varied according to the age of the subject. Children from 5 to 7 years of age received 10 mg three times a day; those from 8 to 15 years received 10 mg three times a day for the first week and 20 mg three times a day thereafter, and those over the age of 15 years received 20 mg three times a day for the first week and 40 mg three times a day thereafter.

Weight was measured at the end of the base-

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Table 1 Observed behaviour in 15 patients with the Prader-Willi syndrome

Food related behaviour
Gorging: placing more food in mouth without swallowing first
Overeating: eating more than usual for age
Stealing food
Eating unusual materials
Aggressive behaviour
Physically aggressive acts
Verbally aggressive acts (including prolonged screaming)
Nagging and other preoccupations
Temper tantrums
Self directed behaviour
Skin picking
Self mutilation (excluding skin picking)

line period and at the end of each treatment period using the same scales and with the subject wearing the same underclothes. Changes in weight were compared using the Wilcoxon signed rank test.

Behaviour was observed throughout the baseline period and the last two weeks of each treatment period. Observers attended a training session before the trial during which they were instructed on how to record their observations of the subject's behaviour (table 1). Observers were unaware of which capsules the subjects were taking. Observation sessions took place at the patients' homes while they were going about their usual activities. The duration of the observation sessions was constant for each subject and always occurred at the same time of the day. Because of differences in family routines, the duration of the daily observation session differed slightly among subjects; it was, however, never less than two hours/day (mean 4.1 hours/day).

For statistical analysis, the number of times each type of behaviour was displayed in one hour was converted into a score using a behaviour rating scale from 0 to 5 (0=behaviour absent, 1=one to five episodes, 2=six to 15 episodes, 3=16 to 20 episodes, 4=21 to 40 episodes, 5=more than 40 episodes; 5 included 'behaviour continually present'). An average daily behaviour score for each type of behaviour was then calculated for the baseline period and for each treatment period. Average daily behaviour scores for related types of behaviour were combined to provide a single pooled score for each of the three groups of behaviour: food related, aggressive, and self directed. The

pooled scores obtained for each patient during treatment with fenfluramine were compared with those obtained while taking placebo using analysis of variance.

Results

Fifteen patients (seven males and eight females) took part, their ages ranged from 5.5 to 27 years, mean 14.2. All patients were overweight and had problems resulting from their hyperphagia and other behaviour. None were receiving medication before the trial, or had any other diseases. One subject was functioning in the average range of intellectual ability, 12 were intellectually mildly disabled, and two were intellectually moderately disabled. The characteristic deletion on chromosome 15 was present in five.

WEIGHT

The weight of one subject was not recorded because of non-compliance. The changes in weight of the other 14 subjects are shown in table 2. Eight subjects lost weight while receiving the drug, while only two subjects lost weight while taking the placebo. The maximum weight loss was 7% (6 kg). For several patients this was the first time they had ever lost weight according to their recorded weights in our clinic records. There was a significant difference between the weight changes during the two periods ($p=0.02$, Wilcoxon signed rank test).

BEHAVIOUR

The behaviour of two patients was not analysed because of incomplete observations resulting from disruption to family routine. The behaviour observation records for the remaining 13 were converted into a pooled behaviour score for each of the three groups of related behaviours (table 3). The higher the score, the more frequently the behaviour occurred. The maximum possible score for either food related or aggressive behaviour was 20, and for self directed behaviour 10.

When these scores were compared using analysis of variance, food related and aggressive behaviour showed significant improvements during the period the drug was being taken

Table 2 Weight changes in patients when receiving placebo and fenfluramine

Case No	When receiving placebo			When receiving fenfluramine		
	Weight before (kg)	Weight after (kg)	Change (%)	Weight before (kg)	Weight after (kg)	Change (%)
1	20.5	20.5	0	20.5	20.5	0
2	98	98	0	98	98.5	+0.5
3	74	74	0	74	78	+5.4
4	62	62	0	62	62	0
5	46	46	0	46	43	-6.5
6	42.5	43	+1.2	43	43	0
7	24	25	+4.2	25	24	-4
8	88	90	+2.3	88.5	88	-0.6
9	48	50	+4.2	49	48	-2
10	18	18	0	18.5	18	-2.8
11	71	70	-1.4	74	71	-4.1
12	20	19	-5	20	20	0
13	92	95	+3.2	94	92	-2.1
14	80	80	0	86	80	-7

Table 3 Pooled behaviour scores for each of the three groups of behaviour measured during the baseline period and when receiving placebo and treatment with fenfluramine

Case No	Food related behaviour			Aggressive behaviour			Self directed behaviour		
	Baseline	Placebo	Fenfluramine	Baseline	Placebo	Fenfluramine	Baseline	Placebo	Fenfluramine
1	0.14	0.07	0	1	0.28	0.35	0.14	0.14	0.64
2	20	6	8.3	0.2	0.5	0	0.51	3.9	10
3	2	0	0.7	3.5	0.2	2	4.2	2.7	1.6
4	1.5	1.4	2.7	6.2	15.2	5	0.57	0.2	1
5	2.1	1.1	0	17	17	0.7	5.5	10	2
6	0.57	0.6	1.2	3.1	2	2.9	0	0	0
7	0.4	0.14	1	9.2	1.0	4.7	1	1.3	4.7
8	0	0	0	0	11.2	10	0	0	1
9	2.4	4	0.5	7.8	15.5	9.3	0.4	5.2	0.57
10	0	0	0	1	2.7	0.4	10	10	9
11	3.2	3.2	0.07	17.7	14.6	11	10	7.6	2.07
12	3.5	2.2	1.07	0.57	0.2	0.2	0.8	0.14	0.28
13	1	2.7	1.8	0.8	2.6	1.3	0	1.6	0.2

($p < 0.05$ and < 0.025 , respectively). There was, however, no significant change in self directed behaviour ($p > 0.10$).

In addition to the changes in scores, parents (and in some cases the patients themselves) frequently reported pronounced qualitative changes during the period the drug was being taken. Some patients quickly realised when they were taking the drug and made statements such as 'these are the real ones'. Some parents reported that this was the first time that they had seen their children refuse food. Some particularly noted behaviour changes, with statements such as 'he is a different child' and 'the best time ever'.

Discussion

Fenfluramine caused significant weight loss and behaviour improvement in some patients with Prader-Willi syndrome, when given for a period of six weeks. Though it is not unexpected that weight loss and improved food related behaviour occurred while the drug was being taken, the reason for the decrease in episodes of aggressive behaviour is less clear. Fenfluramine may have modified this behaviour by reducing the frustration associated with insatiable hunger, or by a direct sedative effect on the brain.¹² The hunger felt by people with Prader-Willi syndrome is similar in some ways to chronic pain, and control of this unpleasant sensation may reduce suffering and frustration even when weight loss is not significantly altered.

We were unable to find any distinguishing characteristics among patients who responded to the drug. The degree of obesity and intellectual impairment did not correlate with weight loss. The presence of the deletion on chromosome 15 also did not seem to play a part. We used a conservative, standardised dose of the drug during this trial, and some patients may require larger doses to control their hunger.

In this study we assessed the effect of a short course of fenfluramine, and suggest that such treatment may be helpful for difficult periods such as holidays, when access to food cannot be

controlled and aggressive behaviour is particularly difficult to contain. It may also be useful in cases of severe obesity in which problems such as poorly controlled diabetes and respiratory acidosis (pickwickian syndrome) make urgent weight loss imperative. Whenever possible fenfluramine should be used in conjunction with other established forms of treatment.

The results of this study raise the question of a possible role for treatment with fenfluramine for periods of longer than six weeks. Long term use of anorexic agents is to be avoided in the management of obesity in general, but it must be remembered that Prader-Willi syndrome is a severe, incurable disorder that takes a devastating toll on affected patients and their families. A double blind placebo controlled trial to determine the efficacy of a longer course of fenfluramine in patients with Prader-Willi syndrome warrants consideration.

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Growth in haemophilic boys after HIV infection

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Abstract

Although failure to thrive has been documented as a major problem in babies with congenital HIV infection, there is little information on whether HIV affects growth in older children who become infected with HIV. The growth of 27 haemophilic boys, in whom HIV seroconversion was recorded between 1981 and 1986, has been assessed to see if the pattern changed after seroconversion. Height and weight recordings were analysed over a mean period of 9.2 years with a mean duration from HIV seroconversion of 4.5 years (range 2 to 6 years). Height standard deviation scores and ratio of weight to 50th centile for chronological age were calculated. No significant change in growth pattern as judged by height and weight has been observed within this group of boys after HIV seroconversion. Growth assessment continues to be evaluated to see if further progression of HIV disease changes growth pattern in these boys.

In congenital HIV infection failure to thrive has been documented as a major problem and an early feature of the disease. In older children, however, many aspects of the natural history of HIV infection remain unclear, particularly with regard to growth and development.

We have studied growth in a cohort of boys with haemophilia A, who have acquired HIV infection through transfusion of factor VIII concentrate, to see if acquisition of HIV infection has altered patterns of growth and development.

Subjects and methods

A total of 27 boys with haemophilia A attending the Birmingham Children's Hospital have been studied. Twenty six of these boys were severely affected and had a concentration of VIII:C less than 0.01 U/ml and one had mild haemophilia with a concentration of VIII:C of 0.05 U/ml. HIV seroconversion was recorded in these boys during the period 1981-6.

As part of their routine follow up since diagnosis each boy is seen in clinic regularly and has had his height (Harpender stadiometer) and weight measured regularly. This has usually been done at least three times each calendar year.

One boy was investigated before HIV seroconversion for constitutional short stature.

At present 10 boys have AIDS related complex and only one boy has progressed to

develop clinical AIDS (one episode of pneumonia caused by *Pneumocystis carinii*). Height standard deviation (SD) scores and ratio of weight to 50th centile for chronological age were calculated using the tables of Tanner *et al* for British children.¹

Mean growth, both height and weight, before and after HIV seroconversion were analysed by the Wilcoxon matched pairs signed rank test and year on year changes in height SD score after HIV seroconversion analysed by paired *t* tests.

Results

Duration of follow up, age, and duration of HIV seropositivity are summarised in the table. The recent seroconversions (two years ago) occurred in boys who had received a dry heated commercial factor VIII concentrate manufactured from plasma that had not been screened for HIV antibody.² Because of these seroconversions this product was withdrawn from the United Kingdom and subsequently from North America and Europe.

In the cohort there was no significant change in growth in height nor weight after HIV seroconversion (figs 1-3). Similarly there was no significant change in year on year change in height SD score after HIV seroconversion, either between consecutive years or at seroconversion and the last year studied.

The one boy who developed AIDS also continued to grow normally along his respective centile (fig 4). Similarly the one boy with constitutional short stature has continued to grow along an acceptable curve parallel, though below, the 3rd centile since seroconversion (fig 5).

Only one boy has failed to continue to grow along his original centile, showing a period of failing growth from the 75-90th to 25-50th centile for height (fig 6). This growth reduction began three years before HIV seroconversion and is probably unrelated to it (fig 7).

Discussion

The normal progression of growth depends on a fine balance of many interrelated factors. Chro-

Data of cohort studied

	Mean (SD)	Range
Duration of follow up (years)	9.2 (2.4)	4-14
Age at time of study (years)	12.8 (3.6)	6-17
Duration of HIV seroconversion (years)	4.5 (1.2)	2-6

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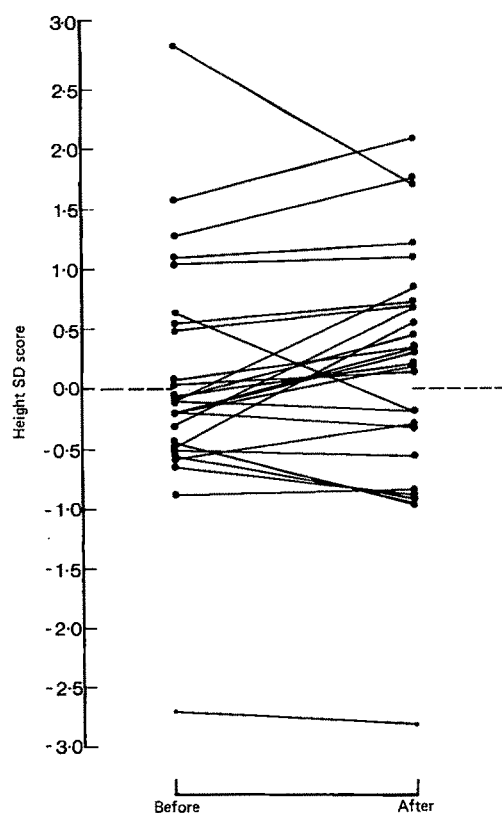


Figure 1 Individual height SD score before and after HIV seroconversion. Note: one boy shows a large fall in height SD score. Despite this fall growth has continued above the 97th centile.

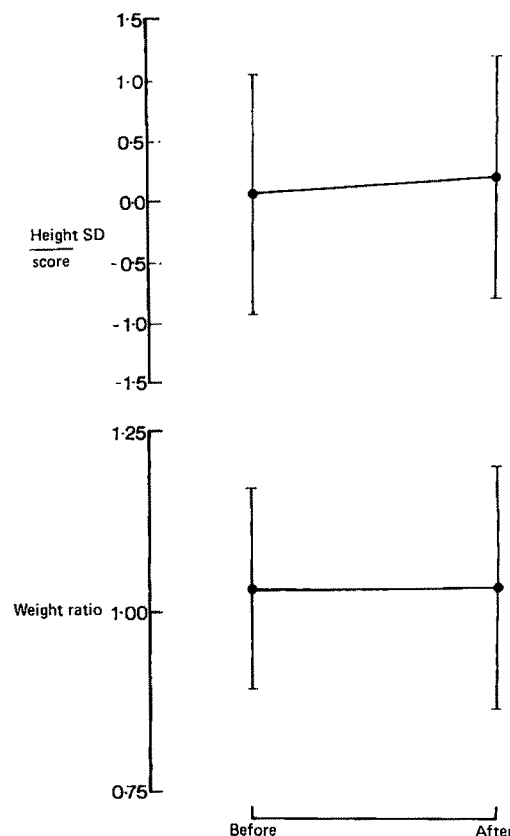


Figure 3 Mean (SD) height SD score and ratio of weight to 50th centile for age before and after HIV seroconversion.

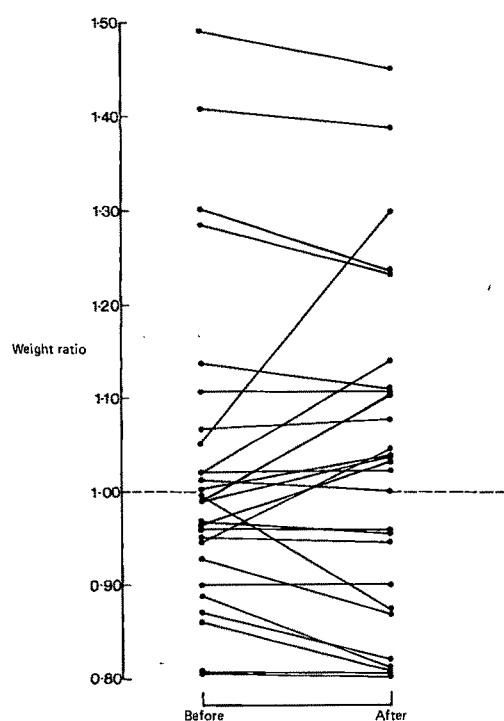


Figure 2 Individual ratio of weight to 50th centile for age before and after HIV seroconversion.

nic illness is well recognised to affect directly and adversely linear growth in situations such as renal failure,³ liver disease,⁴ congenital heart disease,⁴ poorly controlled diabetes mellitus,⁵ and active asthma.⁶

HIV infection can result in a wide range of clinical manifestations, ranging from asymptomatic infection through to profound immunodeficiency characterised by malignancy and opportunistic infection. Growth failure has been described in children with chronic symptomatic HIV infection, AIDS related complex, before the onset of clinical definable AIDS.⁷ Little is known, however, about the effect of asymptomatic chronic HIV infection with regard to growth and development. It has, however, been suggested that growth failure is a feature of chronic HIV infection in haemophilia, though as yet there are no published data to support this.

In the later stages of HIV related disease wasting occurs. No boys in this group studied have yet shown such wasting, presumably as the boys remain relatively well at present, up to six years after seroconversion. This may reflect the relatively better outlook for those who become infected with HIV under the age of 20 years.⁸

The 27 children in this study represent a broad cross section of boys with both symptomatic and asymptomatic HIV infection with infection having been documented for up to six years. In no boy has there been significant growth failure, either of linear growth or body weight, that may be directly attributable to HIV

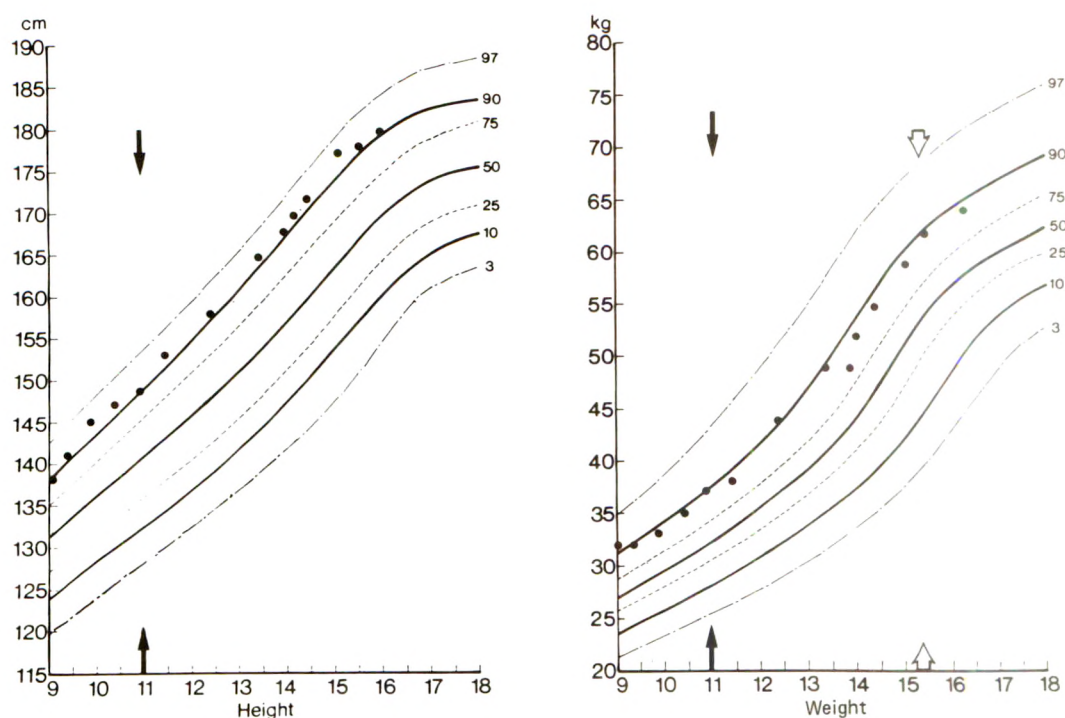


Figure 4 Growth chart, from 9–18 years, of the one boy so far to develop AIDS. Solid arrow represents point of HIV seroconversion. Open arrow represents onset of clinical AIDS. Note: continued progression along the 90th centile.

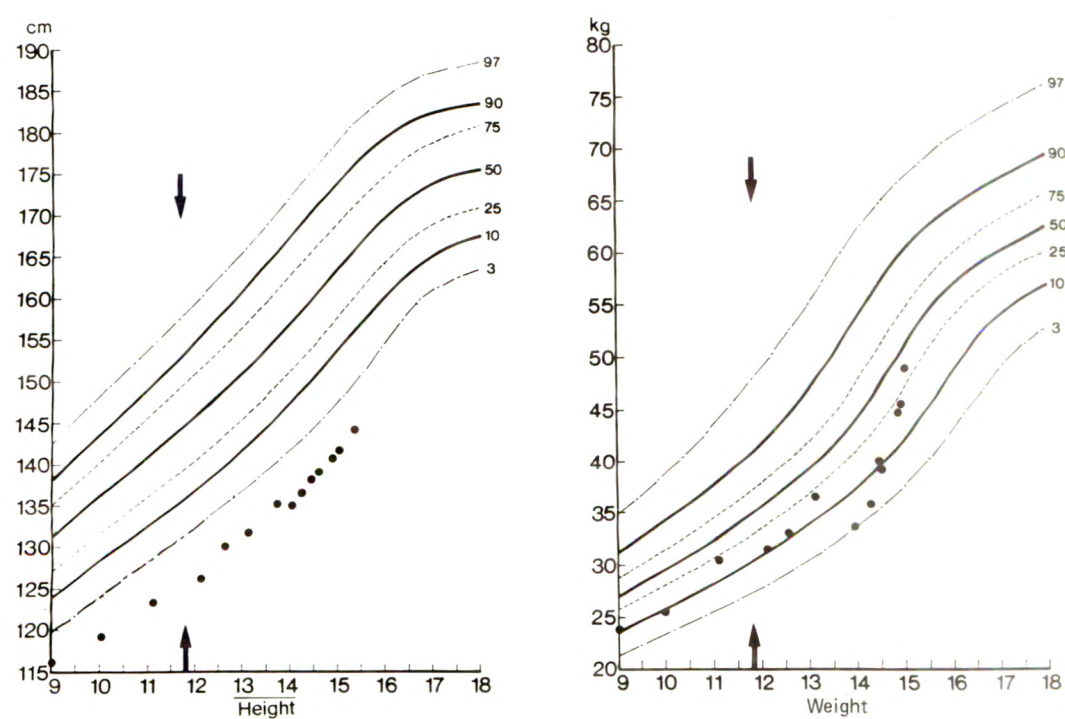


Figure 5 Growth chart, from 9–18 years, of the one boy with constitutional short stature. Arrow represents point of HIV seroconversion. Note: continued acceptable growth along a curve parallel to 3rd centile despite HIV seroconversion.

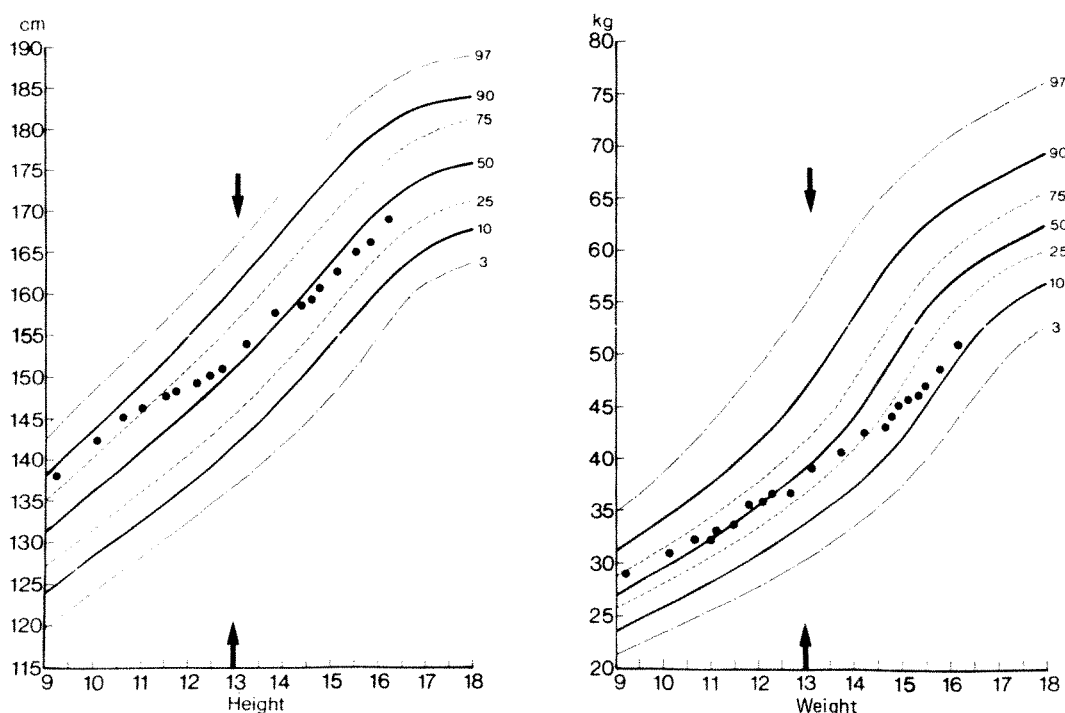


Figure 6 Growth chart, from 9–18 years, of the only boy to show falling growth. Arrow represents point of HIV seroconversion.

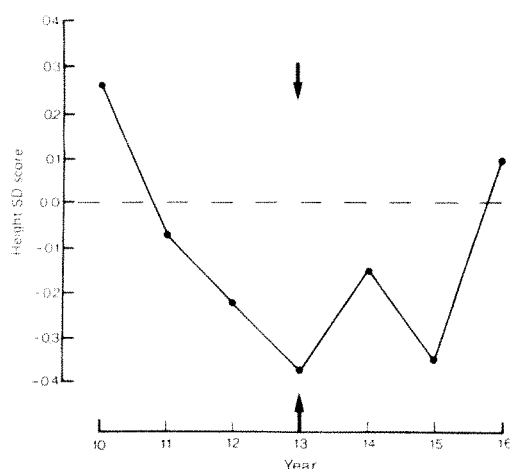


Figure 7 Year on year changes in height SD score for the boy shown in figure 4. Arrow represents time of HIV seroconversion. Note: falling height SD score three years before time of HIV seroconversion.

infection. These boys appear to have continued to grow normally, progressing as expected along their respective centiles for both height and weight. The one boy whose growth did fall off during the study appears to have started to cross the centiles before HIV seroconversion. Without the growth data before HIV seroconversion it would have been easy to have falsely assumed that his fall off in growth was secondary to asymptomatic HIV infection.

HIV infection in haemophilic boys appears to have a modified natural history, perhaps due to the additional immune complications induced by replacement treatment per se. It may be that the apparent preservation of linear growth, up to six years, after seroconversion represents another facet of its differing natural history.

Height and weight continue to be measured regularly in these boys to evaluate whether with time from seroconversion further progression of HIV disease any alteration in growth occurs.

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Sleep habits and height at ages 5 to 11

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Abstract

Shorter durations of slow wave sleep and lower growth hormone responses have been reported in children with short stature caused by psychosocial deprivation. We investigated whether lower total sleep duration was associated with shorter stature in a sample of children taking part in the National Study of Health and Growth. Parental responses to a self administered questionnaire were used to estimate usual times for going to sleep at night and usual times for waking in the morning for 5145 children aged 5 to 11 years of age. After adjusting for the effects of other variables known to be associated with height, it was shown that there was a weak negative association between sleep duration and height. It is concluded that variation in sleep duration between children is unlikely to have an important influence on growth.

Disordered sleep has been reported in children investigated because of short stature.¹ One factor that relates sleep to growth is the diurnal variation in growth hormone secretion: there is a profound increase in circulating growth hormone concentrations during the night,² and this increment is particularly associated with the onset of deep or slow wave sleep.³ In children with short stature caused by psychosocial deprivation, deficient slow wave sleep and reduced growth hormone secretion have been reported^{1,4}; this could contribute to the child's delayed growth. It is not known whether the total sleep duration has a quantitative influence on nocturnal growth hormone secretion or on children's growth. We therefore estimated sleep duration and its relation to height in children taking part in the National Study of Health and Growth. In this paper we report the results of this investigation together with the results of a descriptive analysis of the children's sleep habits and their relation to a number of social and biological variables.

Subjects and methods

The study was performed as part of the National Study of Health and Growth in 1987. This is a survey of schoolchildren aged 5 to 11 years which has taken place annually since 1972.⁵ At each survey the parents are sent a questionnaire to complete and the height, weight, and triceps skinfold thickness of the children are measured.

SUBJECTS

A total of 9913 children took part in the 1987 survey. The sampling procedure has been described previously.⁶ The sample included children from England and Scotland. In England the sample was selected so as to include a high proportion of children from ethnic minority groups or from disadvantaged social backgrounds; in Scotland the sample was representative of the Scottish population.

PROCEDURES

In 1987 the questionnaire used in the study included two questions concerning the child's sleep. These were as follows: (1) at about what time does he or she usually go to sleep at night: (a) before a schoolday? (b) when there is no school the next day? (2) At about what time does he or she usually wake up in the morning: (a) on schooldays? (b) on days when there is no school? Answers were given in hours and minutes.

Parents were also asked to give information about the child's birth weight, the heights of the parents, the number of children in the family, the father's employment state and occupation, and the education of the mother. The number of people in the family divided by the number of rooms occupied (excluding bathroom and kitchen) was used as an index of overcrowding. The ethnic group of the children was classified according to the language spoken at the child's home as well as by the fieldworkers' subjective assessment of the child's ethnic group. This information was used to define the groups: 'Caucasian', Afro-Caribbean, Urdu, Gujarati, Punjabi, other Asian, and 'others'.⁶ The children's heights were measured at school by school nurses supervised by a full time field worker. Height was measured on a portable Holtain stadiometer to the nearest complete 0.1 cm.⁷

ANALYSIS

Mean times for going to sleep and for waking up and mean sleep durations were calculated by age and sex. A height standard deviation (SD) score was calculated for each child by comparing the child's height with the mean and SD for the same age and sex obtained for a representative sample of children measured in 1986. This method of expression standardises for the increased variation in height between the ages of 5 and 11 and removes the effects of age on height. Multiple regression was used to assess the independent effect of sleep duration on

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height.⁸ Independent variables included seven continuous variables: the age and birth weight of the child, the parent's heights, the age of the mother on finishing full time education, the index of overcrowding, and the child's sleep duration. Because of the difference in sleep duration between schooldays and non-schooldays sleep duration was entered as the total duration of sleep during the week (schooldays times five plus weekends times two). Six categorical variables were included: the gender of the child, the number of children in the family, the ethnic group of the child, the country of residence (England or Scotland), the father's social class, and the father's employment state. Social class was divided into five categories: non-manual, skilled manual, semiskilled and unskilled manual, not known or unclassifiable, and a category for children living with a single mother. Father's employment was classified into six groups: employed, unemployed for less than 12 months, unemployed for more than 12 months, unemployed when the length of time was unspecified, not known, and not known when a child was living with a single mother. An interaction term was included to allow for differences in the effects of family size in the different ethnic groups.

Multiple regression was also employed to evaluate the effects of a number of variables on sleep duration. Independent variables included all those defined above except for the child's birth weight and the parent's heights, which were excluded. An interaction term for ethnic group and family size was again included. Mean

values for sleep duration at different levels of categorical variables were estimated by adjusting for the unbalanced distribution of other variables included in the analysis.⁹ Children from Asian backgrounds were grouped as a single class in order to allow estimation of class means.

Results

Height SD scores were obtained on 9140 children aged 5 to 11 years. After exclusion of missing values, complete data for the variables included in the analysis were obtained on 5145 children. The exclusion of cases containing missing values changed the mean height SD score by 0.04 units and the mean sleep duration by two minutes.

Unadjusted mean times for going to sleep, for waking up, and for sleep duration are given by age and sex in tables 1 and 2. It can be seen that sleep habits differ on schooldays and on non-schooldays. Multiple regression showed that five factors were significantly associated with sleep duration: these were the child's age, gender, ethnic group, family size, and social class. Sleep duration was not associated with overcrowding in the home, with paternal unemployment, or with educational attainment of the mother. Adjusted mean sleep durations for schooldays and weekends are given by gender, social class, and ethnic group in table 3. Sleep duration was slightly longer in girls than in boys both on schooldays ($p < 0.01$) and non-

Table 1 Mean (SD) sleep duration by age and sex (hours, minutes)

Age (years)	Sex	No of children	Sleep duration	
			Schoolday	Weekend
5	M	439	11,16 (0,45)	11,06 (0,58)
	F	380	11,17 (0,44)	11,14 (0,55)
6	M	471	11,09 (0,42)	10,55 (0,56)
	F	401	11,08 (0,44)	11,00 (0,52)
7	M	453	10,55 (0,41)	10,44 (0,53)
	F	363	11,01 (0,46)	10,55 (0,58)
8	M	412	10,44 (0,39)	10,40 (0,54)
	F	391	10,50 (0,44)	10,53 (0,59)
9	M	376	10,35 (0,38)	10,30 (0,57)
	F	351	10,41 (0,37)	10,47 (0,55)
10	M	351	10,26 (0,40)	10,29 (0,62)
	F	341	10,23 (0,38)	10,45 (0,55)
11	M	211	10,11 (0,38)	10,26 (0,64)
	F	205	10,20 (0,38)	10,44 (0,58)

Table 3 Adjusted mean (SE) sleep duration on schooldays and at the weekend, by gender, social class, and ethnic group (hours, minutes)

	Sleep duration	
	Schoolday	Weekend
Gender:		
Male	10,42 (0,02)	10,55 (0,03)
Female	10,45 (0,02)	11,07 (0,04)
Social class:		
Non-manual	10,44 (0,04)	10,58 (0,09)
Skilled manual	10,46 (0,04)	11,04 (0,05)
Unskilled manual	10,49 (0,04)	11,05 (0,05)
One parent family	10,47 (0,04)	11,00 (0,05)
Not known	10,25 (0,12)	10,39 (0,17)
Ethnic group:		
White	10,56 (0,02)	10,56 (0,03)
Afro-Caribbean	10,42 (0,04)	10,47 (0,07)
Asian	10,41 (0,02)	11,05 (0,04)
Other	10,42 (0,04)	10,58 (0,05)

Table 2 Mean (SD) times for going to sleep and for waking up by age and sex (hours, minutes)

Age (years)	Sex	No of children	Sleeps		Wakes	
			Schoolday	Weekend	Schoolday	Weekend
5	M	439	20,14 (0,46)	21,01 (0,52)	7,30 (0,32)	8,07 (0,62)
	F	380	20,16 (0,44)	20,57 (0,52)	7,33 (0,28)	8,11 (0,54)
6	M	471	20,24 (0,42)	21,11 (0,47)	7,33 (0,29)	8,07 (0,57)
	F	401	20,24 (0,46)	21,10 (0,51)	7,32 (0,31)	8,10 (0,56)
7	M	453	20,38 (0,41)	21,25 (0,44)	7,32 (0,31)	8,08 (0,58)
	F	363	20,34 (0,40)	21,23 (0,45)	7,35 (0,26)	8,19 (0,58)
8	M	412	20,49 (0,38)	21,32 (0,41)	7,33 (0,26)	8,13 (0,58)
	F	391	20,44 (0,42)	21,30 (0,47)	7,35 (0,28)	8,23 (0,58)
9	M	376	21,01 (0,37)	21,47 (0,45)	7,37 (0,26)	8,17 (0,61)
	F	351	20,55 (0,35)	21,41 (0,40)	7,35 (0,25)	8,28 (0,54)
10	M	351	21,11 (0,38)	21,41 (0,40)	7,35 (0,25)	8,27 (0,60)
	F	341	21,11 (0,35)	21,55 (0,40)	7,34 (0,27)	8,40 (0,58)
11	M	211	21,25 (0,35)	22,10 (0,45)	7,36 (0,29)	8,35 (0,65)
	F	205	21,14 (0,34)	22,05 (0,40)	7,34 (0,25)	8,48 (0,56)

Table 4 Variables associated with height SD scores of children in England and Scotland in multiple regression model

Continuous variable	Coefficient	Standard error	t ratio	Probability
Maternal height	0.042	0.002	21.40	<0.001
Paternal height	0.038	0.002	22.65	<0.001
Birth weight	0.285	0.021	13.35	<0.001
Sleep duration	-0.006	0.003	-2.16	<0.05
Categorical variable	Variance ratio	Degrees of freedom		Probability
Gender	9.07	1,5054		<0.01
Fathers' employment state	2.99	5,5054		<0.05
Ethnic group, family size, and interaction	3.17	61,5054		<0.001

schooldays ($p < 0.001$). The effect was accounted for by earlier times of going to sleep and later times for waking in girls. The social class of the father was not associated with sleep duration on schooldays but at the weekend sleep durations were shorter in children of fathers with non-manual occupations than in children of fathers with manual occupations ($p < 0.01$).

Children of white origin slept for longer on schooldays than children of Afro-Caribbean or Asian origin (table 3). On non-schooldays Asian children showed longer sleep duration but over a seven day week the sleep duration in Afro-Caribbean and Asian children was less than in white children. When the children were considered as a single group, the number of children in the family was not associated with sleep duration on schooldays. However, a significant interaction with the ethnic group of the child was noted. In children of white origin sleep duration increased with increasing family size, whereas in the other ethnic groups there was no consistent effect of family size. On non-schooldays sleep duration increased with family size without a significant difference in trend between the ethnic groups.

Seven variables were significantly associated with the height SD scores of the children, the gender of the child, the father's employment state, the ethnic group of the child, and the number of children in the family as well as the birth weight of the child and his parents' heights. When the total duration of sleep over a seven day week was entered into the model there was a weak negative association between the child's height and the observed sleep duration (table 4).

Discussion

In this study we used parental responses to a self administered questionnaire to estimate the child's sleep duration. Although electroencephalographic measurement of sleep duration is considered to be more accurate than subjective assessment,¹⁰ the use of a sleep questionnaire in normal adults gives results that are correlated with results obtained by the electroencephalographic method.¹¹ In addition, the use of a questionnaire lends itself to use in large scale surveys, which can evaluate the effects of social and other factors on sleep duration and quality throughout the week.¹² In children the use of parental responses may overestimate sleep duration as parents may tend to report times for going to bed and for rising rather than times for going to sleep and waking. We did not

specifically evaluate this effect but present our results in relation to the wording of the question that was asked of the parents.

Despite the social importance of sleep in children, reports containing quantitative information concerning sleep duration in children at different ages are infrequent. Roffwarg *et al* characterised sleep electroencephalographically for a small number of children of different ages,¹³ and these data were subsequently extended by Coble *et al*¹⁴; neither group was able to relate their findings to the social and biological context of the child. In a longitudinal study of 200 Swedish children Klackenberg, using subjective methods, documented the decline in sleep duration from 14 hours per night at 1 year to 10 hours per night at 16 years.¹⁵ The values given over the range of ages are similar to those obtained in a larger sample of British children in the present investigation. Both studies give longer durations for sleep than those reported from electroencephalographic measurement.

In addition to the dominant effect of the child's age in determining the time for going to sleep and for waking, our analysis identified several other factors associated with sleep habits. Effects of gender and social class on sleep habits of older children have been noted previously.¹⁶ In the present study these factors had significant effects that were of small amplitude. Differences in sleep habits between ethnic groups were also demonstrated.

Children from Afro-Caribbean and Asian families slept for significantly shorter durations on schooldays; despite an increase in sleep at the weekend, the total duration of sleep during the week was reduced. This difference was still evident after adjusting for a number of other variables including family size. Previous investigations have suggested that family size is positively associated with later bedtimes and reduced time spent in bed in adolescents.¹⁷ In our sample larger family size was not associated with shorter sleep duration, however, but rather with increased sleep duration in white families only. The different ages of the children investigated in the two samples as well as their different social and ethnic characteristics^{6, 17} might have accounted for this discrepancy. The difference in sleep habits between ethnic groups is thus not accounted for by factors included in the analysis.

Previous analyses of children's height from the National Study of Health and Growth have identified a number of factors that are associated with height in primary schoolchildren.

These include the child's birth weight, the heights of the parents, the ethnic background of the child, and a number of social factors including the father's social class, his employment state, and the number of children in the family.^{6, 18} The association between the gender of the child and height in this analysis resulted from the calculation of height SD scores using data from the representative sample, which results in a different bias in boys than girls.⁶ Recent work has shown that disorders of sleep may be present in children investigated for short stature.¹ This would be consistent with the known association of growth hormone release with slow wave sleep.³ We were therefore interested to examine, in a population sample, the possibility that sleep duration could be associated with height in children of primary school age. After adjusting for confounding variables this analysis showed a weak negative correlation between the child's height and the total duration of sleep over a seven day period. There was therefore no evidence to support an association between longer sleep duration and increased growth. The finding of a weak association between increased height and reduced sleep duration is contrary to our initial hypothesis and is not readily explained. Further investigations would be needed to show whether this is a spurious association or whether identifiable factors influence this pattern of sleep. The findings of this observational study suggest, however, that reduced total sleep duration is not associated with reduced height in a population sample.

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Tracheostomy

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Abstract

The records of all children who had a tracheostomy performed over a 10 year period from January 1979 were reviewed. Altogether 142 patients aged 1 day to 24.8 years received a tracheostomy, 70 in the first year of life. The conditions necessitating tracheostomy were trauma (n=21), acquired subglottic stenosis (n=21), subglottic haemangioma (n=16), Guillain-Barré syndrome (n=14), Pierre Robin syndrome (n=9), craniofacial disorders (n=9), micrognathia (n=5), and others in 47. In patients successfully decannulated the median period of tracheostomy was 104 days (range 3 days to 9.0 years) and in 25 patients the tracheostomy is still in situ. Eighty four patients (60%) were discharged from hospital with their tracheostomy in situ and no patient was kept in hospital because of a tracheostomy beyond four weeks. There were two tracheostomy related deaths in hospital. Both patients had severe acquired subglottic stenosis secondary to ventilation for lung disease of prematurity. There were no tracheostomy related deaths at home; complications included tracheal granulomas and polyps (n=19). After removal of the tracheostomy 13 children had a fistula requiring surgical closure and four required revision of the tracheostomy scar.

Tracheostomy is well tolerated in small children, with few complications and can be managed safely in the home by the family.

Tracheostomy has been practised for 2000 years.¹ The use of tracheostomy is well established in children,^{2,3} although recently its indications and safety have come under scrutiny.^{4,5} Despite many improvements tracheostomies are still associated with significant morbidity and mortality.⁶⁻⁹ The purpose of this review of 142 consecutive tracheostomies performed at the Royal Children's Hospital over a 10 year period was to identify the current indications and morbidity associated with tracheostomy in infants and children.

Patients and methods

The patient records of all children in whom a tracheostomy was performed at the Royal Children's Hospital, Melbourne between 1 January 1979 and the 1 January 1989 were analysed. The Royal Children's Hospital is the main paediatric hospital in the state of Victoria, Australia, serving a population of approximately one million children (0-16 years).¹⁰

During the period studied the technique of tracheostomy remained fairly standard and is still employed. Our routine procedure for elective tracheostomy has involved the placement of an endotracheal tube if one is not already in situ. A sandbag is placed beneath the shoulders to fully extend the neck and head. A transverse skin incision is made 1-2 cm below the cricoid, depending on the size of the child. The subcutaneous tissue and platysma are divided in the line of the incision, and the fascia between the strap muscles divided in the midline. Lateral retraction of the strap muscles exposes the pretracheal fascia. Sometimes the isthmus of the thyroid needs to be retracted superiorly, or divided. Two 3/0 stay sutures are inserted below the second tracheal ring on either side of the midline.

Between the stay sutures a midline vertical incision is made extending through the second, third, and occasionally the fourth tracheal rings using a scalpel. As the endotracheal tube is slowly removed the stay sutures are lifted forward to open the tracheostomy and enable the tracheostomy tube to be inserted. Where applicable, the trocar of the tracheostomy is removed before the tube is connected to the anaesthetic tubing. The tracheostomy tapes are secured around the neck and after closure of the lateral edges of the skin wound, the stay sutures are taped to the anterior chest wall. If accidental displacement and removal of the tracheostomy tube occurs, traction on the stay sutures will facilitate safe reintubation. Postoperatively the patients are nursed in the intensive care unit until the first tube change has been performed on the fifth postoperative day.

When a child is discharged with the tracheostomy in situ, the family becomes primarily responsible for his or her care. Support is offered by a clinical nurse specialist who is based at this hospital and educates the family in tracheostomy care, including recannulation, before discharge and provides a telephone support service. The patients also have regular medical outpatient review. The parents are issued with a portable Laerdal suction unit,

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Table 1 Indications for intubation before tracheostomy

Diagnosis	No of patients (n=97)	Median duration of intubation (days)
Subglottic stenosis	21	15
Head injury	17	10
Guillain-Barré syndrome	14	6
Prematurity	10	76
Pierre Robin syndrome	5	9
Subglottic haemangioma	5	4
Others	25	

which is capable of generating -66.7 kPa (-500 mm Hg) with a free air flow of 32 l/minute and a time constant of 4 seconds. It has a rechargeable battery back up power supply. They use an intercom to monitor the child while it is asleep. Although this responsibility places a heavy burden on the family, this approach allows children to be managed safely in their home environment.

Results

Tracheostomies were performed on 142 patients (82 male, 60 female). Their age ranged from the first day of life to 24.8 years (median age 14 months). The median (range) duration of symptoms before admission was four days (1–1620 days) and before tracheostomy 20 days (1–1626 days). The smallest infant had a weight of 2500 g at the time of tracheostomy. Tracheostomies were performed for congenital airway anomalies in 64 (45%) and for acquired lesions in 78 (55%) of patients.

Ninety seven patients were already intubated before tracheostomy, the indications for which are given in table 1.

About half (70) of the tracheostomy tubes used were Great Ormond Street (J G Franklin and Sons Ltd), 50 were Portex (Portex Limited), seven were Shiley (Shiley Incorporated), and three were metal tubes. In 12 patients (8%) the type of tube could not be determined.

After insertion of the tracheostomy 102 patients received oxygen treatment (median duration five days; range 1–300 days) and 36 patients were ventilated (median 12 days; range 1–316 days). Thirty seven patients received continuous positive airway pressure (CPAP) (median two days; range 1–150 days) with 14 receiving CPAP alone. Of those who were ventilated 14 had Guillian-Barré syndrome and nine required ventilatory support for intracranial trauma, infection, or hypoxia.

The indications for tracheostomy are given in table 2. Ninety six patients (68%) had upper airway obstruction and 45 patients (32%) needed long term ventilation. Of the five patients with croup the median duration of endotracheal intubation before the tracheostomy was 6.5 days (range 1–10 days). Only one tracheostomy was performed as an emergency procedure and no patients have needed a tracheostomy for croup since July 1984. No patients with epiglottitis were managed with a tracheostomy.

There were no significant perioperative complications and no patient was kept in hospital because of the tracheostomy beyond four weeks. Eighty four patients (60%) were discharged with the tube still in situ. Of the 123 survivors 107 (86%) were successfully decannulated with 87 patients (70%) decannulated at the first attempt; 25 patients still have their tracheostomy. In 16 patients decannulation has not been attempted: these patients have a severe head injury, craniofacial anomalies, tracheomalacia, vocal cord paralysis, or congenital or acquired subglottic stenosis awaiting formal surgical correction. The outcome of all patients is shown in table 3.

In the patients who have been successfully decannulated, the median duration of cannulation was 105 days (range 3 days–9.0 years). In those with the tube still in situ the median duration of cannulation (as of 30 April 89) was 2.7 years (range 0.74–9.4 years). In the premature infants who have been successfully extubated the median duration of cannulation was 396 days (range 114–812 days) and of those with the tube in situ the median duration of cannulation was 2.6 years (range 0.8–5.6 years).

Patients aged over 12 months with acquired subglottic stenosis are given laser treatment if the area of stenosis is a circumferential mem-

Table 2 Indications for tracheostomy (n=142)

	No of patients
Acquired subglottic stenosis:	
Premature infants	11
Others	10
Head injury	17
Subglottic haemangioma	16
Guillain-Barré syndrome	14
Craniofacial anomalies	9
Pierre Robin syndrome	8
Vocal cord paralysis	6
Micrognathia	5
Croup	5
Laryngomalacia	4
Laryngeal trauma	4
Brain tumour	4
Cardiorespiratory arrest	3
Tracheomalacia	2
Cystic hygroma	2
Obstructive sleep apnoea	2
Others	20

Table 3 Outcome

	No of patients	Deaths	Decannulation of survivors		
			Successful	Failed	Not attempted
Subglottic stenosis:					
Acquired	21	2*	14	1	4
Congenital	1	0	0	0	1
Head injury	17	3	12	0	2
Subglottic haemangioma	16	0	14	0	2
Guillain-Barré syndrome	14	0	14	0	0
Craniofacial anomalies	9	3	4	2	0
Pierre Robin syndrome	9	1	8	0	0
Micrognathia	5	0	5	0	0
Bilateral vocal cord palsy	6	1	1	3	1
Croup	5	0	5	0	0
Laryngomalacia	4	0	3	0	1
Laryngeal trauma	4	0	2	0	2
Malignancy	7	5	1	1	0
Others	24	4	15	2	3
Total	142	19	98	9	16

*Tracheostomy related deaths (accidental decannulation).

Table 4 Laser treatment

Diagnosis	Decannulation		
	Successful	Failed	Not yet attempted
All patients with acquired subglottic stenosis (n=21)			
Laser	4	3	3*
No laser	7	0	4*
Total	11	3	7
Premature infants with acquired subglottic stenosis (n=11)			
Laser	2	1	3*
No laser	1	0	4*
Total	3	1	7
Subglottic haemangioma (n=16)			
Laser	6	0	1
No laser	8	0	1
Total	14	0	2

*One patient died with the tracheostomy in situ. All patients who failed decannulation were successfully decannulated after laser treatment.

brane no more than 1 cm in depth. Patients with subglottic haemangiomas are given laser treatment if their tracheal lumen is inadequate at 18 months of age and the haemangioma has not showed signs of resolution. The outcome of these patients is shown in table 4.

Five (63%) of patients with the Pierre Robin syndrome failed to achieve an adequate airway after the insertion of nasal tubes or a lip tongue anastomosis, or both. Four (44%) of the patients with craniofacial anomalies subsequently had craniofacial surgery and three are now decannulated. Both patients with tracheomalacia had a tracheo-oesophageal fistula that had been surgically repaired. One patient subsequently had a tracheopexy that allowed decannulation.

There were two patients with obstructive sleep apnoea. One patient with Down's syndrome and severe failure to thrive still had significant upper airway obstruction after adenotonsillectomy. He was successfully decannulated after 18 months when he had achieved normal growth. The second patient with a repaired cleft palate developed obstructive sleep apnoea after a pharyngoplasty and required a tracheostomy, which is still in situ 34 months later.

Complications during cannulation were seen in 19 (13%) patients and included tracheal granulomas (n=14), tracheal polyp (n=1), tracheal diverticulum (n=1), and a paratracheal abscess (n=1). One patient developed bilateral pneumothoraces during replacement of a blocked tube. None of these complications resulted in long term morbidity. A further patient has no tracheal lumen after ignition of anaesthetic gases in his trachea during laser treatment for severe acquired subglottic stenosis.

After successful decannulation tracheostomy related complications occurred in 19 (13%) patients and included surgical closure of a tracheal fistula (n=13), revision of the scar (n=4), tracheal stenosis (n=1), and significant tracheomalacia (n=1). These were significantly more common in patients who had been cannulated with the Great Ormond Street tube ($p<0.001$). These tubes, however, were more commonly used in the younger children.

All the premature infants who required a tracheostomy had upper airway obstruction.

Eleven of the 16 patients had acquired subglottic stenosis, three had subglottic haemangiomas, one had a tracheo-oesophageal fistula with tracheomalacia, and another a laryngeal web. The incidence of complications during cannulation was 31% (tracheal granulomas) and the incidence after tracheostomy was 12.5% (tracheocutaneous fistula requiring surgical closure).

Of the 19 patients who died (table 3), 11 died with the tracheostomy tube in situ. Only two deaths were related to accidental decannulation and both occurred in hospital. Both patients had severe acquired subglottic stenosis secondary to ventilation for lung disease of prematurity. One patient also had cri du chat syndrome. There have been no tracheostomy related deaths at home. The most common causes of death of the other patients were malignancy and severe head injury. There were no deaths of patients with Guillain-Barré syndrome, subglottic haemangioma, obstructive sleep apnoea, croup, or laryngomalacia.

Discussion

The reduction in the incidence of diphtheria since the introduction of a vaccine in 1940,⁵ and the greater use of prolonged nasotracheal intubation for the management of croup and epiglottitis, have led to a decrease in the need for tracheostomy in acute laryngeal infections. Improvements in paediatric intensive care have increased the survival of critically ill children, including premature infants, and therefore there has been an increase in the incidence of tracheostomies in children requiring prolonged intubation. This trend has previously been described.^{5 6 8 9 11 12}

The incidence of successful decannulation at the first attempt was 70%, similar to other studies.^{6 7 9} Swift and Rogers report a 60% success rate with 46% undergoing surgical excision of the tracheostomy stoma at the time of decannulation.⁷ In 22% of these patients post-operative stridor occurred, which was relieved by reopening the stoma in half the patients. In our institution patients are decannulated on the ward after bronchoscopy has been performed to ensure an adequate airway exists. The tracheostomy is not occluded before attempted decannu-

lation nor is the stoma surgically excised. The patients are observed for a further 24–48 hours before discharge. Our results indicate that surgical excision of the stoma is unnecessary as the incidence of successful decannulation is no greater and the postoperative upper airway obstruction is avoided.

In this study the complication rate during cannulation was 13%, lower than reported by other authors.^{6–9 13} After decannulation the incidence of complications is comparable with other studies.^{6 7 9} Over the last decade, prolonged survival of premature infants (gestation <37 weeks) who may require lengthy periods of mechanical ventilation has resulted in an increase in acquired subglottic stenosis.¹⁴ These infants have an increased duration of intubation before tracheostomy and an increased duration of tracheostomy compared with the rest of the study population. This may explain the higher incidence of tracheal granulomas during cannulation. Premature infants with acquired subglottic stenosis have a disappointing rate of successful decannulation despite the use of laser treatment (table 4).

The incidence of tracheostomy related deaths is comparable with other studies that also describe an incidence of about 2%.^{7 8} Both tracheostomy related deaths in this study were due to accidental decannulation, which occurred despite the tube being tied in position. No deaths were due to tube blockage and no deaths occurred at home.

The patients who were discharged with their tracheostomy in situ were discharged from hospital within four weeks of tracheostomy unless there were other conditions that required

ongoing inpatient management. The major difficulties experienced by parents were the frequency of suction and finding qualified people to provide relief care for their child. All children of school age who were neurologically normal were able to attend a normal school with the assistance of an integration aid who was trained by the parents with the support of the clinical nurse specialist.

Tracheostomy is well tolerated in small children, with few complications, and most patients can be safely managed in the home by the family.

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Supraventricular tachycardia in infants: response to initial treatment

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Abstract

All patients with supraventricular tachycardia during the first 12 months of life who presented between 1977 and 1988 were identified by a retrospective survey of records in this hospital and by a questionnaire sent to paediatricians in the Northern region. Twenty two of 29 patients (76%) were in heart failure and seven (24%) had cardiogenic shock. Seven patients (24%) were free of symptoms. All had narrow QRS tachycardia at 215-315 beats/minute (mean (SD) 292 (21)). Initial treatment included digoxin (effective in seven of 14 patients, with overdose in three), verapamil (effective in three of three but fatal in one), cardioversion (effective in all 10 who were treated in this way), iced water applied to the face (effective in all 16 patients on 53 of 59 occasions, 90%). Initial treatment in local hospitals was less effective and associated with more complications than that given in the regional referral centre. Digoxin is often ineffective, return to sinus rhythm is delayed, and overdosing is common. Cardioversion is effective but tachycardia often recurs. Iced water is safe and effective, and should become the treatment of choice for termination of supraventricular tachycardia in neonates and young infants.

Supraventricular tachycardia in early infancy is dangerous and potentially fatal, but if it is diagnosed early and treated appropriately it has an excellent prognosis. Until a few years ago the recommended initial treatment was usually either digoxin or cardioversion. Digoxin, however, was often ineffective, and cardioversion required anaesthesia or sedation and was not easily repeated if the tachycardia recurred. Many newer forms of treatment have been proposed by the authors of standard textbooks on paediatrics including verapamil, disopyramide, and propranolol given intravenously.¹⁻⁴ More recently the dangers of some of these treatments have been recognised, particularly the use of verapamil in neonates.^{5,6} This study assesses the safety and efficacy of initial treatment of tachycardia in infancy.

Patients and methods

The records of all infants presenting with supraventricular tachycardia to the Northern Regional Paediatric Cardiology Unit between October 1977 and November 1988 were reviewed. A questionnaire was sent to all paediatricians working within the Northern region to

identify patients who were not referred to this centre. Infants with prenatal tachycardia that recurred after delivery were included. Those who were treated prenatally but who received no treatment after delivery and had no postnatal recurrence of tachycardia were excluded. Patients whose only arrhythmias were atrial flutter or multifocal atrial tachycardia were also excluded. The clinical history, physical examination, and the electrocardiograms taken during tachycardia and during sinus rhythm were available for all patients. The treatments, their efficacy, and their side effects were recorded. All survivors are still being followed up, but these details are not included as they do not form part of this study.

Application of cold water to the face elicits the 'diving reflex' and produces a temporary pronounced increase in vagal tone, thus slowing atrioventricular conduction and interrupting the tachycardia.⁷ The use of this technique in neonates was first described in 1977 but it is still not widely used.⁸ Application of an ice cold facecloth has been recommended but is often ineffective.⁶ In our experience the best technique is to attach the baby to an electrocardiographic monitor, wrap him in a towel, and then immerse his whole face in iced water for about five seconds. No attempt is made to obstruct the mouth or nostrils as the baby will be temporarily apnoeic. The tachycardia usually stops immediately but cessation may be delayed for two or three seconds or may occur after the baby's head has been removed from the water. It is usually followed by bradycardia, often a nodal escape rhythm, for a few seconds before resumption of normal sinus rhythm.

Results

INCIDENCE

Twenty nine patients who had supraventricular tachycardia during the first 12 months of life were identified. Twenty five of these were seen at the Freeman Hospital, and the remaining four were diagnosed and treated at local hospitals. From 1977 to 1988 the birth rate in the Northern region was relatively constant at about 40 000 live births a year (range 39 350-41 101) giving an incidence of infant supraventricular tachycardia of 1/15 000 live births.

PRESENTATION

All 29 patients presented within the first three months of life and 19 (66%) were seen within the first month. Twenty two (76%) had symptoms and clinical signs of congestive cardiac

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failure. Seven of these were in cardiogenic shock and required active resuscitation. Three had had cardiac arrests in their referring hospitals and although two were successfully resuscitated, both have been left with pronounced developmental or physical problems. The remaining seven patients (24%) were free of symptoms and had no signs of cardiac failure.

ELECTROCARDIOGRAPHY

During tachycardia the surface 12 lead electrocardiogram tracings showed regular, narrow QRS tachycardia in every case, with heart rates varying from 215 to 315/minute (mean (SD) 292 (21)). There was no correlation between heart rate and the presence of symptoms. The tachycardia rate was above 270/minute in all but two patients; they had rates of 215 and 250/minute and were both premature, being born at 32 and 33 weeks' gestation, respectively. Two other babies were born prematurely, at 31 and 32 weeks' gestation respectively, but both had tachycardias of 300/minute. On reversion to sinus rhythm the electrocardiograms showed the ventricular preexcitation that is characteristic of the Wolff-Parkinson-White syndrome in 16 cases (55%); they were normal in the other patients.

INITIAL TREATMENT

Digoxin

Fourteen infants received digoxin initially, seven intravenously and seven intramuscularly. The doses ranged from 25 to 600 µg (8–160 µg/kg) and three patients received appreciable overdoses (375–600 µg). Half reverted to sinus rhythm after a mean of 13 hours (range <1 to 36) and there was early recurrence of tachycardia in three of these. In the remainder, in whom the tachycardia persisted, sinus rhythm was restored either with cardioversion or with iced water applied to the face.

Cardioversion

Sinus rhythm was restored immediately in all 10 babies treated with electrical cardioversion but tachycardia recurred during the same hospital admission in four patients, all of whom had also received digoxin. Cardioversion was performed with 5–50 J. One patient received seven shocks (totalling 140 J), which produced alarming arrhythmias varying from ventricular tachycardia to transient complete heart block during the next few hours.

Verapamil

Three patients were given verapamil. Sinus rhythm was restored in all three but one patient inadvertently received an overdose of 1.5 mg (0.4 mg/kg) resulting in cardiac arrest and death.

Iced water applied to the face

Sixteen patients were treated by application of

ice cold water to the face on 59 occasions. This was mainly by immersion of the face in ice cold water, although ice packs were applied on several occasions. The procedure was effective in restoring sinus rhythm in 53 of 59 attempts (90%) and in all 16 patients. Tachycardia recurred at least once in 11 of the 16 patients (69%). There were no side effects.

Adenosine

One patient was given an intravenous bolus dose of adenosine (100 µg/kg), and sinus rhythm was restored immediately. There were no side effects.

TREATMENT AT THE REFERRING HOSPITAL

Twenty two patients received their initial treatment in the local hospital; most were then referred to Freeman Hospital for further assessment. Fifteen were given digoxin and three (20%) received serious overdoses. Cardioversion was carried out in three patients, one of whom received a serious overdose (see above). Two patients were given verapamil, one of whom died (see above). Nine patients were treated with iced water applied to the face, and sinus rhythm was restored in six (66%). Tachycardia persisted in the other three and sinus rhythm was subsequently restored by further applications of iced water in Freeman Hospital. This result may be accounted for by the district paediatricians' lack of familiarity with the procedure, which can cause anxiety in an inexperienced operator.

OUTCOME

Twenty six of the 29 patients were alive and well at the time of writing. One patient died after being given verapamil. One patient is awaiting renal transplantation for polyuric renal failure secondary to the initial cardiogenic shock. A further patient developed severe cerebral anoxia and now has profound developmental delay. In this last case it is possible, in retrospect, to identify a delay in diagnosis of several hours after presentation to the district hospital.

Discussion

The diagnosis of supraventricular tachycardia in infants is not always straightforward, and its importance is not always fully appreciated. With two exceptions, the heart rates during supraventricular tachycardia in our patients were greater than 270 beats/minute. It may be difficult, however, to differentiate clinically between a tachycardia of 200–240/minute (which may be sinus tachycardia) and a rate of 250 and above, which is always an arrhythmia. For this reason, when there is any doubt, an electrocardiogram should be carried out so that the heart rate can be accurately measured. Some electrocardiographic monitors are unable to count accurately at rates above 220 or 230/minute and should not be relied upon for an accurate measurement of the heart rate.

Two of our patients (both of whom were pre-

mature) had heart rates of 215 and 250/minute, respectively, during tachycardia. This accords with previous reports of lower tachycardia rates in the fetus and in prematurity, although the reason for the difference in heart rates in supraventricular tachycardia between premature babies and those born at full term is unclear.⁹

The ideal treatment for supraventricular tachycardia in early infancy (or for that matter at any age) would be safe, rapidly effective in restoring sinus rhythm, easily carried out or given, free of side effects, and would prevent a recurrence of the tachycardia or be easily repeated if tachycardia recurred. Until fairly recently most patients were treated with intravenous or intramuscular digoxin or with cardioversion. Both of these treatments failed to approach the ideal, but stimulated interest in newer drugs or other forms of treatment.

Digoxin was effective in only half our patients and there was a mean delay of 13 hours before restoration of sinus rhythm. Previous studies have shown that digoxin is effective in up to 87% of patients.¹⁰ In the present study 20% of patients given digoxin in the referring hospital received appreciable overdoses. Miscalculation of paediatric doses of digoxin is a common error, easily made,¹¹ and there is a wide variation in the recommended doses for infants.

Cardioversion when carried out correctly is safe and effective. Recurrence of tachycardia is common, however, and as the procedure is performed under brief general anaesthesia it is not easy to repeat. The dose should be restricted to 0.5–1 J/kg.⁶

The dangers of giving verapamil to infants are now well recognised.^{5,6} Although many patients may be safely and effectively treated with verapamil, the adverse effects are unpredictable and the drug is best avoided in this age group.⁶

Because treatment with iced water has proved to be so effective we have little experience with intravenous adenosine in this age group. Other workers have reported high success rates,

however, low incidences of side effects, and rapid action,¹² but there is an appreciable incidence of recurrence of tachycardia.

In our experience the facial application of iced water, either with an ice pack or by immersion of the face comes close to the ideal form of treatment. It was rapidly effective on 90% of the occasions on which it was attempted, was easily carried out, and was safe with no side effects. Recurrence of tachycardia was fairly common, but the treatment is easy to repeat. The success rate of the procedure was higher in this hospital than in referring hospitals, and with wider experience among general paediatricians it should become the treatment of choice for supraventricular tachycardia in neonates or in early infancy.

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Myopathy with hypophosphatasia

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Abstract

Three children with hypophosphatasia also had muscle pains, stiffness, and symptoms of proximal lower limb muscle weakness that occurred early in the disorder and were the presenting features in two. A non-progressive myopathy may be an important sign of hypophosphatasia.

The clinical features of hypophosphatasia, an inherited metabolic bone disorder, include defective bone mineralisation, skeletal abnormalities, premature cranial synostosis, and premature loss of deciduous teeth.¹ Plasma and tissue activities of the bone/liver/kidney alkaline phosphatase isozyme are low. Urinary excretion and plasma concentrations of phosphoethanolamine and inorganic pyrophosphate are high. Infantile, childhood, and adult forms have been described.¹

We report three unrelated children with a childhood form of hypophosphatasia who also had proximal muscle weakness, a finding not previously recognised as a feature of this disorder.¹

Case reports

CASE 1

This child was first seen at another hospital at the age of 2.5 years because of delayed motor activity milestones, difficulty in walking, and inability to climb stairs; he had mild proximal muscle weakness. Electromyographic examination suggested a muscle disorder and he was thought to have a congenital myopathy. A diagnosis of hypophosphatasia was subsequently made because of abnormal dentition, low serum alkaline phosphatase activity, and severe osteopenia on radiography. We saw him at the age of 5.5 years at which time the motor symptoms were unchanged. In addition, he also complained of pain and stiffness in the leg muscles, more pronounced in the mornings and during cold weather. On examination his height, weight, and head circumference were at the 10th, 5th, and 60th percentiles, respectively, as they had been on previous measurements. He had mild (grade 4/5) proximal muscle weakness, a waddling gait, and difficulty in getting off the floor and in climbing up stairs. The muscles were not tender. Deep tendon reflexes were normal. Serum creatine kinase activity was normal on several occasions. Electromyography showed minor abnormalities compatible with a myopathy. Motor and sensory nerve conduction studies were normal.

When last seen at the age of 9.5 years he still had difficulty in climbing stairs and mild proximal muscle weakness. Muscle pains were no longer severe.

CASE 2

This boy was first seen at the age of 9.5 years because of severe pains in the muscles of his lower limbs. He had had difficulty in walking and climbing stairs since early childhood. On examination his head circumference, height, and weight were at the 75th percentile. He had mild (grade 4/5) proximal muscle weakness, and a waddling gait. He had difficulty in getting off the floor and in climbing up stairs. Deep tendon reflexes were normal. There was no muscle tenderness. Serum creatine kinase activity was normal on several occasions. He had the characteristic radiological and biochemical findings of hypophosphatasia. Electromyography at the ages of 9.5 and 12 years suggested a myopathy. Motor and sensory nerve conduction studies were normal. The muscle pains became less severe when he was about 13 years old, although mild proximal muscle weakness persisted. He was last seen at the age of 17. He no longer had pain, but continued to have difficulty in going up stairs.

CASE 3

This boy was referred for neurological assessment at the age of 3 years because of an awkward gait and muscle pains. His limbs had been floppy when he was an infant. He started to walk when he was 13 months old. He subsequently had difficulty in arising from the floor, and climbing up stairs without support. He was not able to run. He had also been complaining of pain and stiffness in the muscles of his legs since he was 1 year old. The pain and stiffness were particularly severe after physical activity and in damp or cold weather. A diagnosis of hypophosphatasia had been made at the age of 1 year because of premature loss of deciduous teeth and the characteristic biochemical and radiological features. He had also developed craniosynostosis for which craniectomies were performed. On examination his head circumference was at the 40th percentile, and his height and weight were around the 50th percentile. He had mild (grade 4/5) proximal weakness in the lower limbs. Coordination was normal. The muscles were not tender. The deep reflexes were present. He had a positive Gowers' sign and found it difficult to climb stairs without support. His gait was waddling. Serum creatine

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Biochemical findings in three children with hypophosphatasia at different ages (years)

	Serum alkaline phosphatase activity (U/l)	Serum calcium concentration (mmol/l)	Serum phosphate concentration (mmol/l)	Serum creatine kinase activity (U/l)	Urinary phosphoethanolamine concentration (μ mol/mmol creatinine)
Control values	70–258 (1–10 years) 59–422 (10–16 years)	2.0–2.6	1.29–2.26	36–188	<10
Case No 1					
4.5	27	2.4	1.8	107	141
6.5	27	2.4	1.8	80	141
8.5	28	2.4	2.1	100	Not measured
Case No 2					
9	37	2.3	1.9	76	45
13	35	2.5	2.1	Not measured	Not measured
17	17	2.6	1.6	150	Not measured
Case No 3					
1	40	2.4	2.0	Not measured	150
3	57	2.6	1.8	200	Not measured

kinase activity on a random sample was 200 U/l (normal range 36–188). Permission to carry out electromyography and muscle biopsy was refused.

Laboratory investigations

Biochemical findings are summarised in the table.

MUSCLE BIOPSY SPECIMENS

Biopsy specimens of the left quadriceps muscle of case 1 taken at the age of 7.5 years, and the right gastrocnemius and left quadriceps muscles of case 2 taken at the ages of 10 and 14 years, respectively, were examined by light microscopy, histochemistry, and electron microscopy.

The average myofibre diameter was about 60% of normal in case 1 and about 85% of normal in case 2. Isolated small structurally abnormal myofibres were seen in the biopsy specimens from both children.

Discussion

The radiological and biochemical findings in our patients were characteristic of hypophosphatasia. All three had symptoms secondary to proximal lower limb muscle weakness, muscle pains, and stiffness from the time they began to walk. These were the presenting symptoms in cases 1 and 2, and case 1 was initially diagnosed as having a congenital myopathy. Such a presentation has not been reported in hypophosphatasia. Although the possibility of a myopathy was not considered in case 3 when the diagnosis of hypophosphatasia was made at the age of 1 year, the history suggests that muscle impairment was a feature at that time.

The symptoms in our cases could not be explained by skeletal impairment. Their clinical features resemble those in osteomalacia myopathy.^{2–5} Muscle weakness has also been described with phosphate deficiency.⁶ The serum creatine kinase activity is generally normal in osteomalacia myopathy, as it was in two of our three cases. Two of 23 patients

reported by Dastur *et al* had mildly increased serum creatine kinase activity.³ This was slightly raised on a single random sample in our third case, a finding of uncertain relevance. Only minor morphological abnormalities were found in the biopsy specimens of cases 1 and 2. The contrast between the apparently scanty pathological findings, and the more pronounced clinical symptoms in our cases with hypophosphatasia is also a feature of osteomalacia myopathy.⁵ The cause of the myopathy in osteomalacia has not been identified.

We cannot provide a clear explanation for the myopathy in our cases of hypophosphatasia. The precise role of alkaline phosphatase in promoting normal bone formation is still controversial; in general terms, the enzyme hydrolyses monophosphate esters at the epiphyseal plate and in membranous bone. Inorganic phosphate is thereby made available for the formation of hydroxyapatite crystals.¹ Alkaline phosphatase activity has been shown in the walls of capillaries and in the muscular and intimal coats of large vessels, but not in skeletal muscle.⁷ Serum calcium and phosphate concentrations were normal in our patients but it is possible that the intracellular concentration of phosphate was altered in muscles.

A non-progressive proximal myopathy with muscle pains and stiffness may be an important and early sign of hypophosphatasia, which with other osteomalacic syndromes, should be considered in children presenting with such a myopathy.

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Colitis caused by food allergy in infants

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Abstract

Thirteen infants with eosinophilic colitis caused by food allergy were reviewed after five to 10 years. By the age of 5 years most foods were tolerated. The colon was normal in the one child re-examined. There was an atopic association, but no family history of classical inflammatory bowel disease. Allergic colitis is a temporary disorder of early childhood.

Food allergy is important in most children attending hospital with colitis during the first two years of life.¹ The natural history of the disease is uncertain. It might progress to classical inflammatory bowel disease (in particular Crohn's disease) so becoming an intermittent but life long problem, or it may completely resolve (as does food sensitive enteropathy).

The aim of this study was to review the 13 children who have presented to our clinic with colitis caused by food allergy since 1977 who are now over 5 years old.

Patients and methods

Thirteen patients (11 boys and two girls) were studied. All had presented with chronic diarrhoea containing blood and mucus before 2 years of age (median age 2 months, range 1 week-20 months). Four were breast fed by their mothers who were taking normal diets, seven were given cows' milk based formula feeds, and two were given mixed diets. Stool cultures grew no pathogens.

On colonoscopic examination there was patchy colonic erythema in all cases, and histological examination of biopsy specimens from erythematous areas showed inflammatory cell infiltrates in the lamina propria in which eosinophils and plasma cells predominated. One child had a single crypt abscess.

After colonoscopy cows' milk and eggs were excluded from their diets, and the diarrhoea resolved within 48 hours. Seven thrived on soya milk (Cow and Gate formula), but in five symptoms recurred so a chicken based feed (Cow and Gate Chix) was substituted. One continued to breast feed and the mother excluded cows' milk and egg from her diet and took oral sodium cromoglycate. One child also received a short course of hydrocortisone enemas as he had a severe colitis with crypt abscess. Repeat colonoscopies were normal. Early challenge with offending foods was avoided as one child had a severe reaction that required blood transfusion.

Seven of the children (54%) gave a personal, and 12 (92%) gave a family, history of atopy in at least one first degree relative. Symptoms included asthma, eczema, hay fever, urticaria, angio-oedema, and rhinitis, and three had siblings with colitis caused by food allergy. Serum IgA concentration was low in one child and at the low end of the normal range in nine others.

Follow up information obtained at outpatient review included whether symptoms recurred when foods were introduced into the diet, and the age at which offending foods were tolerated. Children were challenged with these foods from 18 months of age, one food at a time. Weight gain was observed, and development of further atopic symptoms recorded. Further investigations included repeat colonoscopy in one patient.

Results

Seven children developed diarrhoea when they were given one or more new foods. The foods were beef (n=3), wheat (n=3), white flour (n=1), fish (n=2), pork (n=2), and goats' milk (n=1). Once established on appropriate diets all children remained healthy and thrived without medication.

Cows' milk was successfully reintroduced to some children between the ages of 18 months and 8 years (median 4) (table). One child did not tolerate it at the age of 2.5 years, and was lost to follow up. Seven children disliked drinking milk, and developed loose stools if they did so excessively, but they tolerated it in cooking.

Most other foods were tolerated over the same age range, but in no specific order, and some are still not tolerated (table).

Colonoscopy was repeated in the first patient diagnosed when tolerating a normal diet and the bowel was macroscopically and histologically normal. Further colonoscopies in the other patients were not clinically indicated.

Two children developed new allergic symptoms (one rhinitis and one asthma), and eczema resolved in six.

Discussion

Food allergy is an important cause of infantile colitis in children referred to our clinic and seems to be benign with an excellent prognosis if treated correctly.¹ The features that distinguish colitis caused by food allergy from classical inflammatory bowel disease are macroscopic appearances at colonoscopy and

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Ages at which particular foods were tolerated by patients who initially presented with colitis caused by food allergy

Case No	Age at time of study (years)	Food introduced	Age at which food tolerated (years)	Food not tolerated at time of study
1	7	Eggs	2	None
2	10	Milk	2.5	None
3	7	Soya, wheat	4	None
4	10	Fish, eggs, milk	7.5	None
5	6	Eggs	4.2	None
6	10	Milk	5.2	Beef
7	8	White flour	3	None
8	5	Eggs	3.6	None
9	7.3	Pork	5	None
10	6.8	Milk	6	None
11	5	Soya	3.5	None
12	5	Milk	4.1	None
		Eggs	5	None
		Eggs	4	None
		Beef	5.2	None
		Soya	5.7	None
		Milk	6.3	None
		Eggs	1.8	None
		Wheat	2	None
		Eggs	3.5	Fish
		Milk	4	None
		Eggs, soya, goats' milk	5.2	None
		Milk	4	None
		Pork, milk, eggs	6	Beef, wheat
		Eggs, milk	4	None
		Soya, eggs, milk	3	None
			3.5	None

histological features of colonic biopsy specimens; complete remission on an appropriate exclusion diet; association with atopy^{1,2}; and no family history of inflammatory bowel disease.¹ Compliance with exclusion diets was apparently excellent, as clinical symptoms and colonic abnormalities resolved completely. Although the typical findings on colonoscopy of patchy, regional erythema and microscopic eosinophilic and plasma cell infiltration of the lamina propria (possibly with oedema) distinguish this condition from other types of colitis, eosinophilic colitis without infection has been described in older age groups. These, however, have not shown immediate resolution of symptoms on exclusion diets.³ Remission of chronic inflammatory bowel disease when taking exclusion diets has been reported, and it is possible that some patients have a chronic colitis caused by food allergy.² The single crypt abscess seen in a colonic biopsy specimen of one infant was probably related to the length of time he had had the disease (eight months),⁴ and has been noted previously in colitis caused by food allergy.⁵

The wide age range over which different foods were tolerated by individual patients meant that the only logical way of reintroducing foods was to offer them at regular intervals, and every six months seemed appropriate. No particular food could be offered first as there was no typical order in which foods were tolerated. Most children tolerated most foods by the age of 5 years (mean age for milk 4.5 years) so they had not yet started school. Variations in the ages at which tolerance was gained was

similar to those of children who 'grow out of' eczema or asthma.

The high incidence of personal or family history of atopy (69% of patients and 92% of first degree relatives) has previously been described,^{2,4,6} as has the unequal sex ratio (11 of 13 patients were boys).⁶ More boys may have low serum IgA concentrations, which is possibly relevant to the pathogenesis of the disease.² The onset while breast feeding and resolution of symptoms with maternal dietary manipulation have also been previously described.^{2,4}

We have shown that colitis caused by food allergy is an eosinophilic colitis in atopic infants. It is well defined, both clinically and histologically, and there is complete remission on an appropriate exclusion diet. It may occur in breast fed babies. The food intolerance seems to be temporary, as by 5 years of age previously offending foods are usually tolerated and all our group could tolerate cows' milk by the age of 8 years. None have relapsed or developed other gastrointestinal problems, particularly classical inflammatory bowel disease.

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Chronic intussusception

A C Page, J F Price, J R Salisbury, E R Howard, J Karani

Abstract

Chronic intussusception is a rare but completely correctable cause of failure to thrive in infants and children. The presenting features differ from acute intussusception. We present the case of a 16 month old boy presenting with a three week history of anorexia, diarrhoea, and weight loss with subsequent delayed diagnosis.

Chronic intussusception, classified as intussusception of chronic onset with a history of greater than 14 days, is more often associated with a predisposing lesion than acute intussusception. Rarely chronic intussusception may present as failure to thrive.¹ The boy presented here, who was investigated for failure to thrive, had an unsuspected chronic intussusception.

Case report

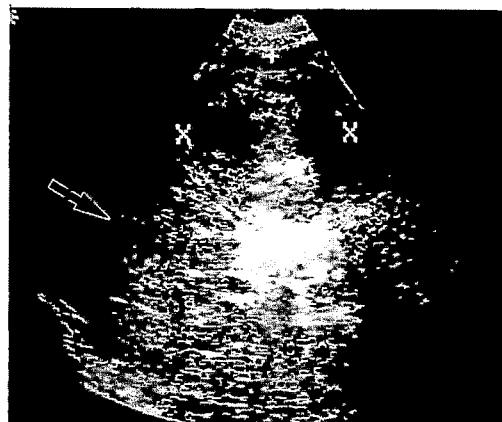
A 16 month old boy presented with a three week history of anorexia, slight cough, diarrhoea, and weight loss. His abdomen was soft and not distended; rectal examination showed yellow stools that did not contain blood. Cultures of the stools, urine, and blood were sterile. A blood count, concentrations of serum ferritin, folate and vitamin B₁₂, electrolytes, urea, and immunoglobulins, activities of liver enzymes, thyroid function, and sweat sodium were normal.

The total serum protein (48 g/l) and serum albumin (28 g/l) concentrations were abnormally low. There was no serological evidence of cytomegalovirus or toxoplasma infection. No autoantibodies or antigliadin antibodies were detected in the blood. A chest radiograph, and a barium meal with examination of the proximal small bowel, showed no abnormality. A cows' milk protein exclusion diet produced only very transient improvement.

Over the next six weeks he continued to lose weight. Despite an estimated intake of 0.42 MJ/day his weight fell from the 50th to below the 3rd centile. He became anaemic (haemoglobin concentration 9.3 g/l), the total serum protein dropped further to 40 g/l and the albumin to 20 g/l.

He was admitted to hospital for further investigation. Occasional vomiting was observed but there was always negligible nasogastric aspirate. A jejunal biopsy specimen was normal. When he was examined under sedation at the time the biopsy was performed, however, an ill defined mass was palpated in the right upper quadrant of the abdomen.

Ultrasound examination of the abdomen demonstrated a subhepatic mass of mixed reflectivity (figure). This was interpreted as a possible duodenal haematoma or a tumour of



Ultrasound examination in the (3.5 MHz probe) showing a longitudinal section in the right upper quadrant. An echogenic mass (marked by crosses) is shown inferior to the liver (arrow).

bowel origin. Free abdominal fluid was seen.

A contrast small bowel examination was conducted to evaluate this suspected bowel associated mass and to determine its site of origin. This showed an intussusception, probably ileocolic coinciding with the mass seen on ultrasound.

At surgery a partially reducible ileocolic chronic intussusception was found extending to the splenic flexure. A 24 cm length of bowel consisting of terminal ileum, appendix, and caecum was resected. The terminal ileum had become invaginated into the caecum to produce an ileocolic intussusception, the apex of which was ulcerated and haemorrhagic.

Histology of the apex showed severe inflammation and ulcerated and partly necrotic lymphoid tissue with follicular hyperplasia. This suggests that an enlarged Peyer's patch may have been the cause of the intussusception.

Postoperatively progress was uncomplicated and six months later the child's weight had returned to the 50th percentile.

Discussion

Chronic intussusception is a rare but treatable cause of failure to thrive. Rafinesque in 1878 recognised a group of children with intussusception who survived greater than 14 days.² He described these as having chronic intussusception. Chronic intussusception now describes cases who present with a history of greater than 14 days at diagnosis. Chronic intussusception defined in this way occurs in approximately 3% of cases under 1 year and 10% over 1 year of age.³ The triad of abdominal pain, vomiting, and bloody stool often associated with an abdominal mass is described as characteristic of acute intussusception but is rare in chronic intussusception.

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Failure to thrive has been described in association with chronic intussusception in one previous report.¹ The authors described three children, aged 10 months to 2.5 years, with clinical histories of seven to 18 weeks' duration. Weight loss and emaciation were described together with abdominal pain and vomiting. Vomiting was a late symptom in our case, and abdominal pain absent.

An unusually high incidence of chronic intussusception and subacute intussusception was described in a study of 62 children from Nigeria.⁴ A high incidence of 'painless intussusception (41%)' was reported. Seven patients with an average age of 5.5 years had a chronic history with a symptom duration of three weeks to three years illustrating the increased incidence of chronic intussusception in the older child.¹ Anorexia, weight loss, and frequent mucoid or bloody stools were the prominent symptoms. This contrasts with our case in which the stools were never mucoid and always occult blood negative.

Incomplete intussusception may be associated with diarrhoea,⁵ and it is possible that the diarrhoea in our case was related to a developing intussusception.

Ultrasound has a recognised place in the diagnosis of intussusception. Although the

identified mass appeared to be related to bowel in our patient, the echo pattern was not characteristic enough to allow a specific diagnosis. In view of the chronic history a bowel associated malignancy was considered more likely.

Barium enema is the investigation of choice in the diagnosis of intussusception and in acute intussusception attempted barium reduction is advocated if the patient is clinically fit.⁶ In the child with failure to thrive and no specific features to suggest intussusception, however, a barium meal and follow through will probably be chosen. The diagnosis will be missed if a barium follow through is not performed.

Chronic intussusception is more commonly associated with a predisposing lesion and operative reduction is the appropriate treatment.¹

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White noise and sleep induction

J A D Spencer, D J Moran, A Lee, D Talbert

Abstract

We studied two groups of 20 neonates, between 2 and 7 days old, in a randomised trial. Sixteen (80%) fell asleep within five minutes in response to white noise compared with only five (25%) who fell asleep spontaneously in the control group. White noise may help mothers settle difficult babies.

Records of intrauterine sounds calm babies and one study found that four out of five infants fell asleep,¹ although the effectiveness of such noise has often been judged solely by the mother.² Quiet sleep in 4 day old neonates was reached significantly sooner and its duration was prolonged by 20% when exposed to continuous white noise.³ We assessed a white noise device, suitable for domestic use and designed to calm babies and promote sleep, by performing a study in which normal neonates were exposed, at random, to a short period of white noise.

Methods

The acoustic output of the commercially available, self contained, battery operated white

noise generator (Babyshh, Egnell-Ameda Ltd) was measured in the acoustic laboratory, Department of Health Supplies Technology Division, Russell Square, London, using the Bruel and Kjoer generating and measuring equipment normally used for assessing deaf aids.

Permission to perform a clinical trial was obtained from the local ethics committee and 40 healthy neonates, born at full term and between 2 and 7 days old, were studied after informed consent had been obtained from the mothers. The white noise device was placed in the cot, between 12 and 20 inches from the baby's head, and either switched on or left off at random according to allocation cards concealed in envelopes. The baby's state was observed continuously for five minutes by a single investigator who noted whether or not the baby was asleep after the four and a half minutes of white noise. Sleep was defined as a state of quiescence with eyes closed and regular breathing.⁴

The first 20 babies had a continuous record of heart rate made during their studies using electrocardiogram electrodes on the chest and an FM7 monitor (Oxford Sonicaid Ltd).

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Characteristics and results of the two groups of neonates

	Exposure to white noise		Significance* (p value)
	Yes (n=20)	No (n=20)	
No (%) of vaginal deliveries	12 (60)	14 (70)	>0.5
No (%) of boys	11 (55)	12 (60)	>0.5
Mean (SD) birth weight (g)	3595 (422)	3531 (453)	>0.5
Mean (SD) age when tested (days)	3.1 (1.9)	2.9 (2.0)	>0.5
Mean (SD) interval since last feed (mins)	43.3 (63.2)	34.0 (34.0)	>0.4
No (%) having breast feeds	6 (30)	7 (35)	>0.5
Effect of white noise:			
No who fell asleep	16 (80)	5 (25)	<0.001
No who stayed awake	4 (20)	15 (75)	

*The groups were compared using the two sample *t* test for means and Fisher's exact test for counts. The effect of white noise was assessed by the χ^2 test.

The two groups were compared using the two sample *t* test and Fisher's exact test. The results, after allocation to white noise or no noise, were evaluated using the χ^2 test and expressed as a relative risk. The number of babies studied was based on an expected three fold increase in the number of babies falling asleep (from 25% to 75%) which would be significant at the 5% level with a power of 95%.

Results

When suspended in the open at a distance of 30 cm (12 inches) the sound intensities measured 72.5 dB for the first 30 seconds and 67 dB for the remaining four minutes. Most of the sound energy lay in the spectral band between 500 Hz and 9 KHz.

Randomisation produced two groups of babies similar in a number of characteristics, as shown in the table. The results of allocation to white noise or no noise are also shown in the table where it can be seen that 16 (80%) babies fell asleep when the device was turned on compared with five (25%) who fell asleep in the control group. This difference was significant ($\chi^2=12.13$, *df*=1, *p*<0.001). The relative risk was 3.2, with a 95% confidence interval of 1.5 to 7.0, indicating that more than three times as many babies fall asleep with the use of white

sound than without it. Of the babies still awake in the control group 11 (73%) fell asleep when the device was switched on, this response rate being similar to the initial results. Two babies in each group were still crying after five minutes and these babies all settled after a feed.

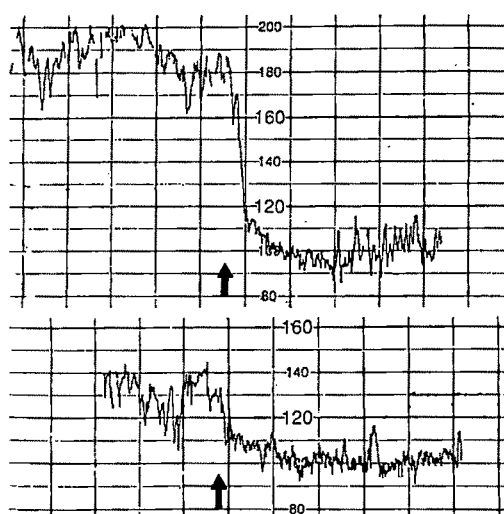
After introduction of the white sound the babies who settled were all asleep within two minutes. The heart rates of the monitored babies who responded settled from between 120 and 180 beats per minute to between 100 and 110 beats per minute, as illustrated in the figure for two of them.

Discussion

The intensities produced by the white noise device used in this study correspond to the noise level of a domestic vacuum cleaner or inside a small saloon car travelling at 50 kph.

This randomised study has shown that, when exposed to white noise, the likelihood of a baby falling asleep is increased more than three fold (25% to 80%). Those that responded did so within a short period of time and before the white noise device ended its emission. Low frequency noise is known to be a more effective inhibitor of behaviour than high frequency sound,⁵ and both continuous and pulsatile sounds have this effect. The noise of hair dryers and vacuum cleaners is known to settle infants and promote sleep. White noise probably acts by masking other external noises thereby removing such arousal stimuli and calming the baby.

We found that white noise promoted sleep only in babies who were not hungry. Two of the babies who did not respond initially settled after a feed. Similarly, two in the control group did not settle when the device was subsequently switched on because they required feeding. Therefore it seems unlikely that use of this device will deprive infants of feeds, should they be required. This is further evidence to suggest that white noise, used for induction of sleep in babies, does not suppress intrinsic stimuli. Total crying time has been found to be related to the method of feeding, such that bottle fed babies cried only two fifths as much as breast fed babies who required complementation by bottle.⁶ Our study of the effect of white noise in promoting sleep in normal neonates suggests it may be of benefit to mothers who have difficulty in settling their baby after a feed.



Two records of neonatal heart rate (vertical divisions = minutes) showing the effect of introducing white noise (arrows). The babies were asleep within two minutes.

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Platelet antigens in varicella associated thrombocytopenia

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Abstract

Serum IgG or, predominantly, IgM antibody binding to electrophoretically separated normal platelet membrane protein antigens were detected by immunoblotting in five children with thrombocytopenia associated with varicella. Glycoproteins GPIb, GPIIb, GPIIIa, and other 25-260 kilodalton (kDa) proteins were identified as target antigens, suggesting a transient autoimmune mechanism causing the thrombocytopenia.

Purpura is a well known complication of varicella but the mechanisms causing thrombocytopenia have not been fully elucidated. Thrombocytopenia may be caused by either immune mediated platelet destruction¹ or direct viral interaction with megakaryocytes or platelets.² Circulating platelet binding antibodies and increased platelet associated immunoglobulins have been described,¹ but the antigenic specificity of the putative platelet binding antibodies has remained unknown. Specific antibodies to defined platelet antigens in thrombocytopenia associated with varicella are reported here.

Patients and methods

Blood was drawn from three boys and two girls, aged 1.5 to 11 years, within a week after onset of purpura, that presented three to seven days after the eruption of a varicella exanthem. All children were previously untreated and in good health. Nadir platelet counts ranged from $2-7 \times 10^9/l$. A bone marrow examination was performed only in case 3 who, after seven days of purpura, had slightly decreased megakaryocytes. Platelet associated immunoglobulins were increased in three out of three tested patients. The chicken pox was in all cases uncomplicated apart from thrombocytopenia, which resolved (platelet count $>150 \times 10^9/l$) within nine to 30 days. Serum samples and normal platelet counts were obtained from four of the children one to seven years later. Sera from 24 healthy blood donors were used as negative controls and anti-PIA¹ sera as positive controls. Separation of

platelet membrane glycoproteins using sodium dodecylsulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and immunoblotting were performed as described elsewhere.³ Briefly, pooled normal platelet membranes were dissolved in SDS and applied to a slab gel together with molecular weight standards. SDS-PAGE was performed under non-reducing conditions using the discontinuous buffer system of Laemmli. The separated proteins were electrophoretically transferred from gels to nitrocellulose membranes and blocked in fat free milk. Membrane strips were incubated with patient or control sera, diluted 1:25. After several washes the blots were first incubated with alkaline phosphatase conjugated protein A or rabbit antihuman IgM and then stained after addition of substrate for the detection of glycoprotein bound antibodies. Glycoproteins were identified on parallel blots by alkaline phosphatase conjugated Lens culinaris lectin which binds to platelet glycoproteins Ib, IIb, and IIIa. To confirm the specificity for platelet surface antigens, sera were absorbed with fresh platelets³ and used in parallel with unabsorbed sera. Sera were also screened with a solid phase platelet membrane enzyme linked immunoadsorbent assay (ELISA).⁴ All positive results were confirmed on repeat testing.

Results

By immunoblotting, platelet glycoprotein binding IgG was detected in sera from three patients and IgM in five patients. IgM corresponded in part to the IgG bands, but additional reactions were noted. The bands comigrated with GPIb (170 kDa), GPIIb (140 kDa), and GPIIIa (95 kDa) in four patients. Other unidentified 25-260 kDa bands were also seen (figure and table). Absorptions of sera with packed platelets eliminated antibody binding to glycoproteins Ib, IIb, IIIa and to the other proteins indicating specificity for native surface antigens. By ELISA, four children were shown to have membrane binding antibodies. In sera collected one to seven years later, the earlier positive reactions were mostly weak or no longer detected (table). In case 4, IgG platelet

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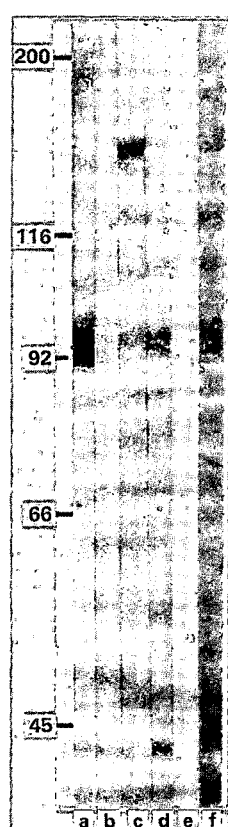
ELISA and immunoblot assays for serum antibodies to platelet antigens in five children with varicella associated purpura and in controls

Case No	Serum sample taken*	Presence (+) or absence (-) of platelet membrane binding antibodies in serum†		Antibodies to SDS-PAGE separated platelet membrane proteins‡	
		IgG	IgM	IgG	IgM
1	During	—	+	38	25, 38, 52
	After (1)	—	—	—	(25), (38)
2	During	ND	+	—	95
	After (1)	—	—	—	(95)
3	During	—	—	25, 38	25, 38, 52, 170, 260
	After (4)	—	—	—	(52), (260)
4	During	+	+	—	38, 95
	After	ND	ND	ND	ND
5	During	+	+	95, 140	38, 52, 95
	After (7)	—	—	—	38
Controls (n=24)		—	—	—	—

*Sera were collected during thrombocytopenia and in the convalescent period (No of years after thrombocytopenia).

†ELISA.

‡Bands detected by immunoblotting; molecular weights of target antigens in kDa. Parentheses denote a weak reaction. ND=not done.



IgG and IgM antibodies to SDS-PAGE separated platelet membrane glycoprotein antigens as detected by immunoblotting in patient and control sera. Apparent molecular weights are given in kDa. Lanes a, b, and c show platelet antibodies of IgG class and lanes d, e, and f of the IgM class. Lane a was incubated with Pl^{A1} antiserum. The Pl^{A1} alloantigen is situated on GPIIIa (95 kDa). Lanes b and e, normal sera; c and d, case 5. The 140 kDa band in lane c comigrated with GPIIb. Lane f, case 2.

membrane antibody was detected in the ELISA but not by immunoblotting. IgG-F(ab')₂ binding to GPIIb/IIIa could be confirmed as previously described.⁴

Discussion

Various mechanisms underlying the virus associated thrombocytopenias have been proposed. Non-immunological factors such as viral interaction with platelets or megakaryo-

cytes have been suggested when purpura presents in the viraemic phase of varicella,⁴ while the 'postinfectious' purpura would more likely be immune mediated. Increased megakaryocyte counts may, however, be found in patients with thrombocytopenia presenting early during the exanthematous phase. Feusner *et al* reported shortened platelet survival, increased megakaryocyte counts, and platelet binding antibodies in serum and on platelets in four children with varicella associated thrombocytopenia, indicating an immune mediated platelet destruction.¹

IgG antibodies directed to platelet membrane glycoprotein antigens have been shown in chronic idiopathic thrombocytopenic purpura, confirming the autoimmune nature of that disease.⁵ Few data have been available about the pathogenesis of acute idiopathic thrombocytopenic purpura. Recently antibodies to platelet membrane glycoproteins have been observed,³ and also binding via the IgG F(ab')₂ part to the GPIIb/GPIIIa complex in patients with acute idiopathic thrombocytopenic purpura.⁴ The present finding of IgG and predominantly IgM antibodies directed to platelet surface glycoproteins, including GPIb, GPIIb, and GPIIIa, during active disease suggests that they may have a role as a thrombocytopenic factor in these varicella patients. The presence of HLA or alloantibodies is unlikely in the untransfused children. In ELISA, with a different antigen presentation, platelet membrane antibodies were detected in four patients. The course of thrombocytopenia might be connected with the primary IgM antibody response to an infection. Varicella zoster virus appears in the blood five days before the onset of a rash. Elicited antiviral IgG is detectable in serum three days after exanthem, by which time the viraemic phase is concluded.⁶ An early thrombocytopenia could be mediated by IgM class platelet cross reactive antibodies or antibodies produced by unspecifically stimulated autoreactive B lymphocytes. It is concluded that the detection of platelet antigen reactive autoantibodies strengthens the concept of a transient autoimmune platelet destruction in children with chicken pox induced thrombocytopenia.

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Is a specialist paediatric diabetic clinic better?

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Abstract

Diabetic control in 88 children attending three general paediatric clinics was compared prospectively over one year with that of 89 children attending a specialist paediatric diabetic clinic. Glycated haemoglobin (HbA₁) concentration and days admitted were significantly lower in the group attending the specialist clinic. This has implications for the organisation of paediatric diabetic services.

Diabetic control in many children is not as good as it could be.¹ It has been suggested that better diabetic control is achieved in children attending specialist paediatric diabetic clinics,² but few objective studies have been done. We have collected, over a one year period, data about diabetic control in children attending a specialist paediatric diabetic clinic in a children's hospital compared with those attending paediatric clinics in three district general hospitals.

Methods

The diabetic clinic at the Royal Hospital for Sick Children (RHSC) acts as a primary referral centre for children under 16 years in south east Scotland. It is staffed by three paediatricians (two consultants and one senior registrar), one adult diabetologist who facilitates gradual transfer of adolescents to the adult clinics, a dietitian, a full time nurse specialist, and a dental hygienist. There is 24 hour access by telephone to medical or nursing staff for advice and the specialist nurse visits at home as required.

Three general paediatric clinics (A, B, and C) in district general hospitals in central Scotland provide care for diabetic children who are seen by a consultant paediatrician or paediatric

registrar. A dietitian is available in all these clinics, and a diabetes nurse specialist who is shared part time with the local adult clinics is sometimes available.

Information about children under 13 years of age on 1 October 1985, and with diabetes of more than three months duration, was obtained prospectively for one year as part of a research project concerning diabetes education. Data included a medical and social profile, methods of diabetic care, diabetic events, anthropometric measurements, and measurement of glycated haemoglobin (HbA₁) at each visit. (All blood samples for HbA₁ were analysed at RHSC by a Corning electrophoretic method; the normal reference range is 4.7-7.9%. Samples were analysed within one week and remained stable.³)

Data from the three district general hospitals and the RHSC clinic were compared by χ^2 or Kruskal-Wallis tests as appropriate, and associations between quantitative and ordinal variables were tested by Kendall rank correlation.

Results

Comparisons were made at the end of one year (a) between the three general paediatric clinic populations, and (b) for all these three clinics combined (if there was no significant difference between them) with the RHSC paediatric diabetic clinic. Age, duration of disease, age at diagnosis, the number of boys, and social class distribution were similar (table 1). The average time spent with the paediatrician at each clinic visit was 25 minutes at RHSC and approximately 15 minutes in the general clinics.

Children attending the clinic at RHSC were admitted to hospital for significantly fewer days

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Table 1 Characteristics of diabetic children <13 years of age attending paediatric clinics in district general hospitals (A, B, C) and a specialist paediatric diabetic clinic (RHSC)

	A (n=40)	B (n=24)	C (n=24)	RHSC (n=89)
Mean (SD) age (years)	10.7 (2.6)	11.1 (1.9)	10.2 (2.4)	10.6 (2.8)
Mean (SD) duration diabetes (years)	4.2 (2.5)	4.9 (2.8)	3.3 (1.7)	4.6 (2.8)
Male/female	16/24	10/14	7/17	39/50
No in social class I and II	13	6	12	32

There was no significant difference between groups for any variable.

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Table 2 Comparison of indices of diabetic control between RHSC and three general paediatric clinics over a one year period

	A (n=40)	B (n=24)	C (n=24)	p Value*	RHSC (n=89)	p Value†
Mean (SD) No of days admitted/year	2.7 (6.8)	3.1 (6.0)	2.4 (4.4)	NS	1.2 (5.8)	<0.05
No (%) patients admitted for hypoglycaemia	6 (15)	0	0	<0.05	14 (16)	NT
No (%) patients admitted for hyperglycaemia	7 (17)	8 (33)	8 (33)	NS	3 (3)	<0.001
Mean (SD) HbA _{1c} (%)	12.0 (2.6)	12.1 (3.0)	11.2 (1.9)	NS	10.3 (1.6)	<0.001
Mean (SD) No of clinic visits/year	5.7 (1.7)	6.1 (2.5)	4.3 (1.6)	<0.001	4.8 (1.2)	NT
Mean (SD) insulin dose (U/kg/24 hours)	0.92 (0.2)	0.95 (0.3)	0.90 (0.2)	NS	0.91 (0.2)	NS
No (%) patients with two injections/day	35 (87)	11 (46)	14 (58)	<0.01	81 (91)	NT
No (%) patients with two insulins/day	32 (80)	8 (33)	23 (96)	<0.01	84 (94)	NT

*Comparison between the three general paediatric clinics.

†Comparison of the three general clinics combined compared with RHSC clinic.

NT=not tested because of a significant difference when comparing A, B, and C.

(table 2) and those admitted for poor control and hyperglycaemia were also significantly fewer. There was a significant difference between the three general paediatric clinics in the number of children admitted with hypoglycaemia. Mean HbA_{1c} concentration for the year was similar for children attending each of the general paediatric clinics but significantly lower in those attending the RHSC clinic.

Daily insulin dose was similar for all children but methods of administration differed. Two injections per day were used more by children attending clinic A, and two different insulins per day (that is, short and intermediate acting insulin) as opposed to one insulin per day (intermediate acting) were used more often by children attending clinic C. Fewer clinic attendances per year were made by children attending clinic C. Attendance rate at all clinics was greater than 80%. Anthropometric measurements including growth velocities were not significantly different between groups and were within the normal range.

Discussion

We have observed in diabetic children who were similar in age, duration of diabetes, and social class, that diabetic control was better in those attending a specialist paediatric diabetic clinic than in those attending general paediatric clinics. Control in children attending the general clinics was in fact not dissimilar from that reported previously from another specialist centre.¹ The introduction of a specialist clinic in East Birmingham where none previously existed resulted in a dramatic improvement in diabetic control.²

What are the possible explanations for the better control achieved by the specialist paediatric diabetic clinic? The number of clinic visits to the specialist clinic at RHSC were significantly fewer and the time spent with the doctor was not significantly different in comparison with the general clinics. Access to a paediatrician with a special interest in diabetes may be beneficial, but the diabetes team he leads might

be a more important factor. This includes specialist nurses, both in the ward and clinic, whose roles are supportive and educational, a dietitian with specific expertise in diabetes, and a dental hygienist. All play a part in educating and motivating families towards good control and are often more accessible than medical staff.

The standard of control achieved, however, may not be commensurate with the greater resources available in the specialist centre, but the introduction of some aspects of specialist care into district general hospitals—for example, the specialist nurse—and shared care between centres may produce savings in both hospital admissions and future complications. Thus the specialist clinic can act as an advisory, educational, and training resource for other clinics. The annual incidence of insulin dependent diabetes mellitus has almost doubled in a decade in Scotland,⁴ a trend found in most developed countries,⁵ and these young people will place an increasing burden on health care resources. The evidence that good control can reduce future complications is growing,⁶ and their incidence may be reduced if diabetic children can achieve optimal control.

We thank Drs Blair, Barclay, Whyte, McAlinsh, and Campbell for permission to study their patients, Miss E Wilkinson and Mrs UL Ursula Grant for extensive help with data collection, and Dr Rob Elton for help with statistical analysis. Dr Susan Bloomfield was funded by a Project Development Grant from the British Diabetic Association.

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CONTROVERSY—*reviews of a book*

Health for all children

Health for all children. Edited by David Hall. (Pp 134; £5.95 paperback.) Oxford Medical Publications, 1989. ISBN 0-19-261815-6.

We find it hard to detect anything here of a genuine thought out philosophy. The title is 'Health for all children' but the book is largely concerned with the identification of defects. The proposals are muddled and contradictory.

The first muddle is 'screening'. The working party persist in using the term screening as a synonym for the detection of abnormality while claiming to be scientific in their approach for surveillance. In recent years screening has taken on a restrictive meaning for certain very limited types of test for specific disorders and criteria for these tests have been established (quoted by the working party pp 8-9). Most medical activity is not encompassed in these very strict criteria and the working party give no reasons why they should be applied to the task of child health surveillance. They admit that even anthropometric measurement 'must not be regarded as simple screening tests. Skill and judgment are required in deciding how to interpret the measures and no single fail/pass criterion can be proposed' (p 46). Yet in their recommended core programme of health surveillance they italicise measurement of height, weight, and head circumference as *fulfilling the criteria for screening tests* (p 99). Physical examination, checks for testicular descent, and auscultation of the heart are similarly classified not withstanding the skill and judgment required to interpret these procedures. How much more are skill and judgment necessary for the various tests and observations we make of developmental aspects of the child such as in the assessment of speech and language. The Hall report says 'Developmental examination is a term applied to a set of procedures which usually includes a developmental history, observation of the child's behaviour, the administration of various tests in order to establish a stage of development of an individual child, to recognise deviations from normal'. They then say 'Developmental screening involves the performance of developmental examination'. They then use the strict screening criteria, for example, to reject identification of children with speech and language disorders, saying that there are no effective treatments for speech and language disorders—incidentally not true anyway (see for example, Nye *et al*¹) but even if it were they are using the screening criteria to reject the identification of disabling conditions. This terrible muddle about screening, examination, and surveillance should have been clearly sorted out at the beginning of the book and it would not then have led them to make daft statements like (p 70) 'We do not think any of the methods of developmental screening can meet the requirements for a screening test'. As they are not screening tests of course they don't.

The next muddle: a serious misquotation is on p 72 when they say 'Although routine developmental examinations are capable of detecting extreme deviations from normal development, most serious impairments are found by other means'. The statement is backed by reference 45. We had been watching out for it, and it is to Drillien and

Drummond's outstanding work.² Actually what Drillien and Drummond said was that the *very* (our italics) severe disabilities could be picked out in this way. This might seem a small error but isn't if you have studied the Drillien and Drummond book. 'Very severe' is one category under which the authors categorise their cases, the others are severe, moderately severe, moderate, and minor. There are of course a number of children—15 in this study of over 4000 children—who do have *very* severe defects, which indeed we would all pick out and so would their parents. However, many of the children with severe problems were as Drillien and Drummond make clear, picked out by the surveillance programme (77%). The best thing to do here perhaps is to quote what the authors said in conclusion to that study:

'Our study also suggests that there exists, in the preschool population a body of pathology that is largely unrecognised and untreated by either primary care practitioners or hospital-based consultants'.

Chapter 12 deals with psychiatric disorders in the preschool population, and also in a final paragraph in the school age child, in just over a page and a half. We think this chapter can only be described as pathetic and indeed the whole tone of it implies that the authors would be quite happy if psychiatric disorders would go away: '7% of three year old children are said to show moderate or severe adjustments problems'. There is no reference after that statement but presumably they were thinking perhaps of some of the work in the Richmond, Stevenson, Graham study which they seem to disregard. Ignoring this sort of study they say there are close parallels between screening for psychiatric disorder and developmental screening. Clearly in their mind there are because they then say quite dogmatically 'behavioural screening questionnaires should not be used routinely'. No support for this statement, just another Hall dogma.

Finally perhaps their material about parents, which again is so sparse as to be absurd. They draw attention to the fact that parents want to be informed and play a part in developmental surveillance of their children. The writers of this report see this as a change over the last 20 years. It would be good if they could have written something about some of the profound social changes that have taken place in the last 20 years and which have such implications for anyone planning a surveillance programme. We refer to the issues of inner city parents, the increase in one parent families, large numbers of immigrants coming from cultures very different to our own, etc, etc. If you are working in Bradford or in London you do have to think about these issues. Health authorities have a responsibility for the health care of *all* children, not just a majority; so to prepare a national pattern of surveillance that depends heavily on a hunch unsupported by factual evidence that the parents of a majority of children can be relied upon to spot significant defects (however covert), is unsound. Many among the remaining minority of children will inevitably miss out.

For these and other reasons we regard this report as a

disastrous failure and cannot recommend it to authorities planning a surveillance service.

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- 1 Nye C, Foster SH, Seaman D. Effectiveness of language intervention with the language/learning disabled. *J Speech Hear Disord* 1987;52:348-57.
- 2 Drillien C, Drummond M. *Development screening and the child with special needs. A population study of 5000 children*. London: Spastics International Medical Publications, 1983.

It is laudable that at last, representatives of all professional bodies concerned with child health, having taken expert advice from many sources, have finally come together to produce a report on child health surveillance. This in itself is an achievement and long overdue. Any such consensus report is likely to be of value. The report is comprehensive and yet clearly and concisely written. It is true that some of the recommendations are controversial and these have generated anxiety. My own initial response was a cautious welcome: the report requires careful reading and, with time to reflect, I commend the principles of the working party.

As stated by Dr David Hall, one must acknowledge the contribution of the pioneers of child health and development over the last 20 years, but the time has come to use their expertise to develop a more appropriate service for the 1990s. The case for reappraisal is clearly made in the report; some activities may indeed lead to unnecessary parental worry and be unpopular with the consumer, who should now be heard. The 1981 Education Act has happily reduced the need for detailed developmental screening to categorise or label children.

The attempt to define and clarify terms such as surveillance, screening, and assessment is lucid and I feel can be applied to child health, although others disagree. Few would argue about the importance of early detection of certain disorders, the need for an active surveillance programme, or the contribution made by parents to this process.

Being mainly research based, the sections on physical examination and laboratory screening do not appear controversial. The approach to child psychiatry and the emphasis on the importance of health education and promotion, although not proved, reflects a balanced view.

The recommendations on growth measurements and their recording seem to me, a non-expert, a reasonable compromise in the light of available data. As the report suggests, regular weighing reassures parents and professionals but is perhaps of less benefit to the child.

The general comments on vision and hearing screening are sound and in particular, the need for meticulous training. The recommendations on vision are imprecise, however, and perhaps districts should await further research before abandoning the preschool visual acuity test.

Throughout the report the need for research in child health surveillance is emphasised, which I wholeheartedly endorse. In busy district child health departments, however, time, money, and methodological expertise is often lacking despite the enthusiasm.

The section on screening for developmental impairments has caused the most controversy among professionals in the field, but I sympathise with the working party's view that

routine detailed developmental screening is unnecessary. Experienced practitioners will detect abnormal development by the commonsense approach; that is by listening to parents, taking proper histories, and observing children at play. Nevertheless I believe that the trainees will still learn best by the developmental check lists. The important subject of training is well addressed in some considerable detail.

I commend any worker in the child health field to read this report. It must be remembered that modifications will be necessary in the light of new research and papers presented at the British Paediatric Association annual meeting this year have already brought into question two of the recommendations.

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There are three reasons why I think this report should be read in detail by all paediatricians.

(1) It is a scholarly report. Read in conjunction with Butler's report,¹ it is the best analysis, from this country or abroad, of the principles and detail relevant to the health surveillance of children.

(2) The report is directly relevant to the United Kingdom. It takes account of the organisation of primary care in this country. The committee members, unanimous in their report, represent the British Paediatric Association, the British Medical Association, the Health Visitors' Association, the Royal College of General Practitioners, and the Royal College of Nursing. Further the Secretary of State for Health, both in his forward to the report and in his proposed contract for general practitioners, supports the report and intends that it be implemented.

(3) There is much to be gained by implementing the report's recommendations across the country. Such a programme could be evaluated. The surveillance of children who change districts would not be disrupted. Training programmes for nurses and doctors could be standardised. The alternative is for each district or primary health care team to continue to adhere to its own judgments and prejudices in the vain hope that it has found the perfect programme and can implement and evaluate it.

When reading the report, try not to relate it too much to your own experience and views. The committee recognises that there are some uncertainties about surveillance that the scientific evidence cannot yet resolve and where therefore it had to make a 'best buy' judgment. Even enthusiasts for frequent, detailed developmental examinations of preschool children recognise that there is little evidence, for or against, what they do. It is important that what is of proved value is delivered to all children. In the present state of knowledge, the emphasis should rightly be shifted from repeated, detailed examinations of children who happen to come to a clinic to the systematic examination of *all* children using a small number of tests uniformly applied.

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CURRENT TOPIC

Renal transplantation

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End stage renal disease is a rare condition in children. It has a prevalence of 20-50 children under the age of 15 years per million child population in those European countries with the largest population. The loss of renal function progresses through several stages defined by clinical characteristics and related to the degree of remaining residual function. Chronic renal insufficiency defines the stage in which residual function has not fallen to less than 30% of normal. Chronic renal failure describes renal function less than 30% with a residual potential glomerular filtration rate less than 15% of normal. End stage renal failure defines the point at which dialysis treatment or renal transplantation begins.

The causes of primary renal disease leading to chronic renal failure vary according to country. In general, however, congenital and familial conditions are more common than acquired renal disease. Reflux nephropathy (pyelonephritis) and some form of renal dysplasia or anatomical defect are responsible for more than 50% of cases, whereas acquired glomerulonephritis accounts for up to 30%.

Data presented in the 17th Combined Report on Regular Dialysis and Transplantation of Children in Europe confirmed the rapid development of continuous ambulatory peritoneal dialysis used in 23% of patients who commenced treatment for end stage renal disease in 1986, compared with 10% in 1981.¹ As the first method of treatment of end stage renal failure, however, renal transplantation increased from 2 to only 5% over the same period. Nevertheless it is encouraging to read that almost 50% of all children on the registry file aged less than 15 years at the end of 1986 had a functioning renal allograft. Taken from the same report actuarial survival for patients engrafted between 1983 and 1986 showed an 87% survival at three years for live related donor kidneys and 65% for cadaveric grafts. These figures reflected the wide ranging results obtained in the many centres surveyed, as a consequence of variations in clinical practice especially in the use of immunosuppressive drugs. Recent analysis from centres in the United Kingdom using comparable clinical management and immunosuppressive regimens would suggest at least an 80% graft survival of first cadaver donor kidneys at one year and virtually 100% success for live related donor grafts.^{2,3}

Renal transplantation has therefore become firmly established as the preferred treatment for children suffering from end stage renal failure.

There are many major differences between paediatric and adult renal transplantation. Foremost is the primary cause of renal failure, with a high incidence of children in whom there is urological abnormality. Before renal transplantation, the recipient native kidneys are removed only in exceptional circumstances. Intractable nephrotic syndrome, severe arterial hypertension, and infection associated with vesicoureteric reflux that cannot be managed by medical treatment are such examples.

Recognition that an adult donor kidney can be safely engrafted intra-abdominally in very small infants has necessitated the use of large more proximal recipient blood vessels such as the aorta and inferior vena cava.⁴ Although adult cadaver kidneys are more readily available, the use of paediatric organs is preferable. The high incidence of complications with kidneys from infants less than 2 years of age, however, especially arterial and venous thrombosis, argues against their use.

Increasing experience in the perioperative management and meticulous attention to fluid and electrolyte balance has reduced the problem of intratransplant sequestration and drainage of a significant proportion of the blood volume and cardiac output of a small recipient, after vascular anastomosis. This has significantly reduced graft loss secondary to arterial or venous thrombosis.⁵

The greater emphasis in some centres on living related donor allografts, has resulted in substantial improvement in outcome with renal transplantation in recipients under the age of 30 months.⁶ Results are acceptable and therefore may not justify a prolonged wait for a small cadaveric kidney.

The controversial question, Should kidney transplants ever be performed in the first year of life in those children born with renal failure? is frequently asked. The answer is never clear, is always controversial, and confounded by ethical issues concerned with infant bonding and psychomotor development during the first year of life. There are undoubtedly some infants for whom extending life by dialysis and transplantation is not in the best interests of the patient or their family. However, in the face of technical advance the decision not to treat is always a difficult one. Current trends in some paediatric renal units in the United Kingdom would suggest that up to 25% of the population with end stage renal failure is under 5 years of age. This together with a prevailing move towards transplantation before a dialysis requirement has been realised places enormous demands on

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the carers. Only a constant and improving supply of cadaver donor kidneys can guarantee that advances will be made in this area.

Patient preparation before transplant

Review of the results of cadaveric renal allograft survival would suggest that there is little universal agreement as to the selection of the best available human leucocyte antigen (HLA) match, that is, tissue typing.⁷ Indeed the efficacy of HLA matching is controversial. At any moment in time the demand for cadaveric organs exceeds supply and it is therefore rarely feasible for many transplant units to pay strict attention to HLA matching. Immunological damage to the renal allograft is mediated by both humoral and cellular mechanisms. Acute humoral rejection results in a vasculitic catastrophe occurring when kidneys are transplanted into hosts in whom preformed cytotoxic antibodies exist, targeted against the blood groups ABO or HLA associated antigens present in the transplanted organ.⁸ Chronic humoral rejection is also principally targeted against graft endothelium and invariably leads to inexorable graft loss. Rejection pathways are initiated by activation of a population of recipient antidonor T lymphocyte clones that recognise donor histocompatibility antigens in the graft. Humoral rejection is refractory to current antirejection treatment and may indeed be ultimately best treated by prevention through accurate—that is, complete—tissue matching.

Therefore on the day of transplantation a cross match test is mandatory. ABO typing and cross matches between recent and historic recipient serum and donor T and B lymphocytes are obtained in order to exclude the presence of preformed recipient antidonor, class I HLA cytotoxic antibodies capable of producing acute humoral rejection. Class I antigens coded for by the A, B, and C loci, are glycoproteins detected on all cells of the transplantable organs, and peripheral blood lymphocytes are the best readily available source of cells for testing. The distribution of class II or DR antigens is confined primarily to endothelium and the dendritic cells in most lymphoid tissue. The total time for HLA typing is between four and six hours, and conceptually matching as a means of improving graft survival is attractive as incompatibility for these antigens may well be the major stimulus for the generation of the immune response against a renal allograft.⁹

Immunosuppression

No consensus has developed on how to achieve optimal immunosuppression, and indeed many individual centres employing different protocols report excellent results for both graft and patient survival. A biological approach to immunosuppression is mandatory, using several agents simultaneously each of which is directed at a different mechanism of activation of allograft rejection. Triple or quadruple immunosuppression using corticosteroids, azathioprine, cyclosporin, and a polyclonal antibody have

become standard practice. Their benefit allows for the use of a low dosage of each individual agent, thus obtaining maximum immunosuppressive benefit with minimal toxicity. Detailed discussion of individual dosage regimens is beyond the scope of this review but a brief description of each immunosuppressive agent is given.

Prednisolone used from the time of transplantation interferes with T cell activation by blocking the signals mediated by the lymphokine interleukin I, and remains the potent drug in preventing early acute rejection. Cyclosporin, now in clinical use for almost 10 years, blocks the elaboration and release of interleukin II thus depriving the activated T cell of the stimulus necessary to sustain activation. The antimetabolite azathioprine is the nitroimidazole derivative of 6-mercaptopurine and is used to inhibit both DNA and RNA synthesis. This drug will therefore inhibit cell proliferation of those lymphocytes not already affected by prednisolone and cyclosporin. Low dosage prednisolone, cyclosporin, and azathioprine are probably ineffective in blocking the activity of already activated T cells and thus these drugs are relatively incapable of suppressing an already established acute rejection. Polyclonal antibody preparations such as antithymocyte globulin are therefore used as antirejection prophylaxis in many centres. Monoclonal preparations directed against specific components of the human T lymphocyte complex are still experimental and experience to date is restricted to their use in adult patients.¹⁰

The principal target of cyclosporin is the kidney itself and nephrotoxicity can occur at any time in the post transplant period. The early reversible form of toxicity leads to decreased blood flow because of vasoconstriction; failure to reduce the dosage promptly may result in more permanent damage characterised by interstitial fibrosis and glomerulosclerosis.¹¹ Cyclosporin is strongly lipophilic and thus measured therapeutic concentrations correlate poorly with toxicity in some patients. Renal injury secondary to other nephrotoxic drugs or acute renal failure may potentiate the toxic effects of cyclosporin. Extrarenal complications include tremor, gingival hypertrophy, and hirsutism, the latter particularly troublesome in children.

Allograft rejection

The clinical signs and symptoms of acute rejection are protean but are likely to include fever, swelling and tenderness of the graft, hypertension, oliguria, and a measurable deterioration in renal function. The histopathology of cellular rejection is characterised by a dense infiltration of T cells within the medullary regions of the graft. Allograft rejection remains the single most common cause of graft loss for any group of renal transplant recipients. Fortunately most acute cellular rejection episodes respond to bolus corticosteroid treatment, more resistant rejection may respond to antithymocyte globulin. This is a polyclonal antibody preparation derived from either a

horse or rabbit immunised with human lymphocytes. The antibodies are not specific, although directed primarily against lymphocytes. Its value in treating steroid resistant rejection is well established even though adverse reactions including anaphylaxis, thrombocytopenia, neutropenia, and phlebitis are common.

Future developments

The disease from which a recipient of an allografted kidney develops renal failure may affect the outcome in two ways. Firstly, the disease may be such that the recipient's life is threatened, alternatively the grafting may be put in jeopardy by the recurrence of the original disease in the grafted kidney.¹² For Wilms' tumour transplantation within one year of native nephrectomy was associated with a recurrence of disseminated disease. Patient survival with bilateral tumours may be as low as 38%, death being associated with infection, perhaps aggravated by chemotherapy and irradiation.¹³ The recurrence of certain types of glomerulonephritis remains a problem. Lesions of focal segmental glomerulosclerosis and a nephrotic syndrome may recur in almost a quarter of all cases especially in those children in whom there was a rapid onset of renal failure. Improved techniques for the early diagnosis of infection in the immunocompromised patient and a better understanding of the transmission of glomerulonephritis are clearly needed to improve both patient and graft survival in this group. Uncorrected congenital abnormalities of bladder storage and abnormal bladder emptying (for example, posterior urethral valves) also appear to adversely affect graft survival.^{14 15} An earlier understanding of bladder physiology could improve the results in these patients.

Anti-HLA antibodies may occur as a result of a failed transplant or blood transfusions and persist in high titres for many years. Approximately 20 to 30% of patients in the United Kingdom, of whom few are children, currently awaiting renal transplantation have these antibodies. These patients are classified as highly sensitised and are thus difficult to transplant. Preventing sensitisation by the transplantation of a well matched live related or cadaver donor kidney without HLA antigens against which the recipient has made antibodies would be ideal but is not feasible given the poor supply of cadaveric organs.¹⁶ Strategies for the removal of anti-HLA antibodies using plasma exchange and immunosuppression are potentially useful but remain experimental and have a risk of antibody resynthesis.¹⁷

The ideal immunosuppressive strategy for tissue transplantation is one that permits the development of long term immunologic tolerance with minimal interference with normal body processes. With more careful prescription the side effects of prednisolone and cyclosporin have become less of a clinical problem, although they remain significant. The future must rest on the production of a natural human antilymphocyte monoclonal antibody.

The management of children with end stage renal disease is frequently complicated by

growth retardation and renal osteodystrophy. The concept that growth potential at the time of transplantation, as indicated by bone age, is an important factor for growth after transplant, and that recipients with a bone age greater than 12 years grow minimally despite successful transplantation has been challenged¹⁸ as post-pubertal recipients had significant height increment after transplantation. Impaired linear growth therefore reflects several factors including growth potential achieved at the time of transplant, poor allograft function, and corticosteroid dosage required for immunosuppression. Poor linear growth before transplantation undoubtedly has a great influence on adult height. However, the loss of growth potential during pubertal development may be even more important.¹⁹ Evaluation of the development of hormonal changes during puberty is needed in order to further understand the characteristics of growth.

In addition to concerns about growth retardation and pubertal delay, children who receive transplants must also cope with the tasks of growing emotionally and psychologically. Evidence of low esteem, defective social adaptation, and non-compliance with immunosuppression is present in many children assessed by child psychiatrists and supported by skilled social workers.²⁰ There is no doubt that the quality of life of a transplant recipient is far superior to that of a dialysis patient, but that quality is not ideal. Medicines must be taken daily in order to prevent rejection, hospital attendances are necessary for physical examination and blood tests, and admission to hospital to treat complications of transplant surgery and the side effects of immunosuppression are not uncommon. Ultimately all renal transplant recipients must live with the uncertainty that their graft might fail at any time and this has been compared with the 'Damocles syndrome' often encountered in the treatment of patients with malignant disease.²¹ The high rate of psychiatric morbidity in children with end stage renal failure and their parents is intimately linked to the fact that most families have coping difficulties, and suggests the need for skilled intervention.

Renal transplantation is technically feasible and is successful for most children. Of approximately 3500 potential renal transplant recipients currently listed on the United Kingdom Transplant Register, 80 are children under 16 years. The challenges that remain to all involved in the care of the children with end stage renal failure are not only to provide a therapeutic environment that will ensure good quality of life but also to guarantee that the present level of service can be maintained.

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ANNUAL STATISTICAL REVIEW

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This is the third in the series of annual reviews of national statistics relevant to childhood. Statistical data are provided which will allow updating of most of the tables in the annual statistical review of 1988 and will enable the reader to examine trends. Where entirely new data are provided it is hoped that, by stating the source publication, the reader can obtain previous years' data if trends are the object of interest.

Natality

The number of births in the United Kingdom rose further in 1987 to 775 600 births, an increase of 2% over the previous year. Among these births, 22.9% were outside marriage, this

also was an increase from 21.4% in 1986. The key birth statistics for United Kingdom and constituent countries are given in table 1. In England and Wales, the increase in the proportion of births outside marriage was predominantly among jointly registered births.

Counter to the overall increase in number of births in the 1980s, there has been a decrease in births to mothers whose country of birth is in the Indian subcontinent or the Caribbean (table 2).

Mortality**INFANT MORTALITY**

The infant mortality rates for 1987 and the provisional rates for 1988 for England, Scotland, and Wales are shown in table 3. The rise in the infant mortality rate for England and Wales in 1986, which engendered considerable public concern, once again assumed a downward trend. The improvement in infant mortality during the 1980s is, for England and Wales, almost entirely attributable to the reduction in neonatal mortality. Postneonatal mortality fails to show any significant change, which is probably an indictment of social policy in relation to children. This pattern is not found in Scotland where the downward trend is also evident in postneonatal mortality rates.

A new neonatal death certificate was introduced on 1 January 1986 that allows certifiers to state both maternal and fetal conditions which contributed to the death. As equal weighting is given to main conditions in the fetus and in the mothers, it is no longer possible to identify a single cause of death for neonatal deaths and comparisons with the period before 1986 will not be valid.

This restriction does not apply to postneonatal deaths but as neither the postneonatal mortality rate nor its constituent causes of death groups has altered in any significant way, in 1987, the trend over time does not require special comment.

Table 1 Key birth statistics for United Kingdom and constituent countries 1987

Country	No of live births (thousands)	General fertility rate*	Births outside marriage (%)
United Kingdom	775.6	62.3	22.9
England	643.3	62.0	23.2
Scotland	66.2	58.8	22.8
Wales	37.8	62.9	23.3
Northern Ireland	27.9	82.2	14.3

*Births per 1000 women aged 15-44.
Source: OPCS Series FMI No 16, 1987.

Table 2 Live births by country of birth of mother (Great Britain)

Area or country of birth of mother	Live births (thousands)			
	1971	1981	1986	1987
United Kingdom	773.3	617.3	641.9	663.8
Republic of Ireland	22.5	8.6	6.4	6.2
Old Commonwealth	2.7	2.6	2.7	2.8
India	13.7	12.6	10.8	10.2
Pakistan and Bangladesh	8.5	17.0	18.9	18.3
Caribbean	12.6	6.3	4.7	4.6
Other New Commonwealth	11.4	18.7	19.8	19.9
Other European and rest of the world	20.4	20.2	21.4	21.8
Total with mothers born outside United Kingdom	91.8	86.0	84.8	83.9

Source: Social Trends 19, 1989.

Table 3 Infant mortality rates 1987 and 1988*

Country	Perinatal mortality†		Neonatal mortality‡		Postneonatal mortality‡		Infant mortality‡	
	1987	1988	1987	1988	1987	1988	1987	1988
England	8.9	8.7	5.0	4.9	4.1	4.1	9.1	9.1
Scotland	8.9	9.0	4.7	4.6	3.8	3.6	8.5	8.2
Wales	9.2	8.3	5.0	4.7	4.5	2.9	9.5	7.6

*1988 provisional.

†Per 1000 total births (live and still).

‡Per 1000 live births.

Source: Population Trends 1989;56:50-1.

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Table 4 Death rates/100 000 for all causes of death among children 1-19 years of age, by country, age, and sex: selected countries, 1985

Country	1-4 Years		5-9 Years		10-14 Years		15-19 Years	
	Male	Female	Male	Female	Male	Female	Male	Female
England and Wales	49.8	40.8	21.6	18.1	28.9	18.7	67.6	28.2
United States	58.1	44.5	28.2	21.2	34.9	20.5	114.7	46.5
Federal Republic of Germany	46.7	42.2	24.4	22.1	22.7	16.6	83.4	33.9
France	49.4	41.3	28.3	21.1	29.6	18.5	89.3	39.3
The Netherlands	45.5	37.5	21.1	13.6	22.2	13.9	60.2	24.9
Sweden	30.0	28.4	19.6	10.5	17.2	15.1	61.6	30.8
Canada	47.8	37.3	26.4	18.7	31.2	20.3	101.7	42.1
Japan	55.7	41.6	26.6	15.3	19.9	13.1	69.8	23.7
Australia	56.6	45.0	29.6	19.9	28.7	16.0	111.5	41.7

Source: United States Department of Health and Human Services. Vital Statistics series 3, No 26, 1989.

Table 5 Children aged under 16 by social class of head of household, Great Britain 1971 and 1981

Social class of head of household	Children in each social class (%)		Change in numbers of children 1971-81 (%)
	1971	1981	
I Professional, etc	5.9	6.0	-19.2
II Intermediate	18.7	23.3	-1.0
III Skilled, non-manual	10.0	10.3	-17.9
III Skilled, manual	39.1	36.2	-26.3
IV Partly skilled	16.2	15.3	-24.9
V Unskilled	6.8	5.2	-38.8
Armed forces and inadequately described	3.2	3.6	-10.2

Source: Britain's Children. OPCS Census Guide No 2.

CHILDHOOD MORTALITY

International comparisons of mortality among children are shown in table 4. It can be seen that the rates for England and Wales tend to be in the middle of a ranking table. That does not provide grounds for complacency, however, because the tragedy is that so many of the deaths are preventable. In the age groups 5-9 and 10-14, about two fifths of the deaths are due to accidents. The scope for prevention is evident from the very striking social class differences in mortality due to accidents whether they be motor vehicle traffic accidents, accidents caused by fire and flames, or by submersion, suffocation, etc.

MORTALITY AND SOCIAL CLASS

Statistics of infant mortality in England and Wales in relation to parents' occupation and

social class were first presented for the year 1911. Deaths of children under school leaving age by social class is a more recent development dating from the Decennial Supplement to the 1931 census. Now for the first time such statistics have been published in a separate volume.¹

The proportion of children in the different social classes has changed with a relative increase in the upper social classes and a decrease in the lower social classes. This is partly due to a general upward drift towards more highly skilled occupations and partly because there has been a disproportionately greater reduction in births to the lower social classes between 1971 and 1981. These data are given in table 5. The drift towards the higher social classes also makes for problems in comparing trends in social class mortality over time. Because of social class differences in mortality and morbidity, these trends are of relevance to child health.

The social class differences in mortality during infancy and childhood are shown in table 6. The greatest differential in both boys and girls is during the toddler years 1-4 and in the postneonatal period. In this table the data for infants comes from the linkage of birth and death registration documents which has been routine since 1978. For children aged 1-15 years, the numerator deaths are also obtained from the registration procedure but the denominator population numbers are from the 1981 census.

In comparing social class mortality rates for children the group missing from table 6 is the

Table 6 Mortality of children aged under 15: rates/100 000 by age, sex, and social class in England and Wales 1979-80, 1982-3

Sex and social class	Age at death					
	Stillbirth	Neonatal	Postneonatal	1-4 Years	5-9 Years	10-14 Years
Males						
I	483.6	556.9	309.8	33.0	24.2	20.5
II	558.9	637.3	327.2	34.2	19.0	21.9
III non-manual	564.3	685.1	323.4	41.3	22.9	20.3
III manual	715.0	733.3	419.4	52.7	25.9	26.3
IV	847.3	935.6	574.6	63.8	31.7	30.5
V	919.0	1055.4	759.3	111.5	50.1	36.2
I-V ratio	1.90	1.90	2.45	3.38	2.07	1.77
Females						
I	420.4	429.8	254.2	33.1	16.5	15.1
II	529.5	489.8	272.5	31.2	15.1	15.4
III non-manual	603.0	537.8	278.8	35.8	17.5	14.0
III manual	673.6	570.5	331.1	42.0	18.3	19.1
IV	809.4	720.6	450.8	52.2	22.6	17.4
V	805.6	737.9	588.4	85.6	30.6	23.9
I-V ratio	1.92	1.71	2.31	2.58	1.85	1.58

Source: OPCS: Series DS, No 8, 1989.

'other' category. This includes those who are 'unoccupied' and in 'inadequately described' occupations. The last named category includes many women who are single parents, separated, divorced, or widowed. The significance of the 'other' category becomes evident when cause of death in the postneonatal period is examined by social class (table 7). This category now constitutes an underclass and consistently fares less well than social class V. The relative risk is particularly high for the sudden infant death syndrome and deaths due to accidents. The increasing proportion of children now allocated to the 'other' category makes the interpretation of social class trends in childhood mortality difficult.

BIRTHWEIGHT SPECIFIC MORTALITY

Table 8 updates the birthweight specific mortality table from the last annual statistical review. Continuing developments in neonatal

intensive care have led to an increased interest in the fate of extremely low birthweight infants (≤ 1000 g). To enable the reader to examine mortality trends, data are presented in table 9 which subdivides the infants of birth weight ≤ 1500 g into ≤ 1000 g and 1001–1500 g.

Since 1 April 1987 information on low birthweight infants has been collected by the Department of Health for a financial rather than a calendar year so the most recent data cover the period 1 April 1987 – 31 March 1988. In April 1988 the old form LHS 27/1 with birthweight notifications was replaced by the Korner form KC52.

The striking observation shown in table 9 is the increase in late neonatal mortality for the extremely low birthweight infants between 1976 and 1981. This suggests that many deaths were postponed from the early neonatal (first week) to the late neonatal (second to fourth week) period. The overall neonatal mortality rate showed a continuous improvement from 1976 to

Table 7 Postneonatal mortality rates/100 000 live births by cause of death and social class in England and Wales 1979–80, 82–83

Cause of death	Total	Social class						
		I	II	III (non-manual)	III (manual)	IV	V	Others
Congenital anomalies (ICD 740–759)	79.7	65.3	66.9	65.2	78.2	95.3	104.6	130.0
Conditions originating in the perinatal period (ICD 760–779)	17.8	13.7	15.5	15.0	15.6	25.7	21.4	29.7
Sudden infant death syndrome (ICD 798)	140.8	98.6	103.9	92.5	133.9	172.4	245.6	333.0
Accidental (ICD E800–E999)	19.8	11.9	9.8	14.2	15.6	24.0	41.6	95.8

ICD: International Classification of Diseases.
Source: OPCS: Series DS, No 8, 1989.

Table 8 Birthweight specific mortality for England and Wales, 1987

	Total	Birth weight (g)							Not stated
		<1500	1500–1999	2000–2499	2500–2999	3000–3499	3500–3999	>4000	
Stillbirth*	5.0	127.3	59.9	15.7	4.6	1.6	1.1	1.7	61.7
Perinatal*	8.9	301.4	86.5	22.4	6.5	2.6	1.9	2.7	246.7
Neonatal†	5.0	239.0	36.1	8.9	2.9	1.4	1.1	1.3	223.1
Postneonatal†	4.0	32.1	17.2	9.2	5.5	3.0	2.5	2.4	23.9
Infant†	9.0	271.2	53.3	18.1	8.4	4.4	3.6	3.7	247.0

*Rate/1000 total births; †rate/1000 live births.
Source: OPCS DH3 (volume to be published).

Table 9 Birthweight specific mortality: very low birthweight infants (≤ 1500 g), England only

Year	Stillbirth rate*	Perinatal mortality rate*	Early neonatal mortality rate†	Late neonatal mortality rate†	Neonatal mortality rate†
<i>Birth weight ≤ 1000 g</i>					
1976	353.2	818.7	719.7	38.2	758.0
1981	285.1	679.2	551.3	65.4	616.7
1982	239.9	649.1	538.3	63.6	601.9
1983	224.5	601.2	485.7	57.1	542.8
1984	214.2	570.2	453.1	53.6	506.7
1985	209.4	579.0	467.5	52.9	520.4
1986	204.5	542.1	424.3	52.9	477.2
1987/8	190.0	520.1	407.5	68.0	475.5
<i>Birth weight 1001–1500 g</i>					
1976	275.5	491.5	298.1	27.4	325.5
1981	177.4	297.8	145.8	28.0	173.8
1982	159.9	280.0	143.0	29.2	172.2
1983	149.0	254.2	123.6	24.1	147.7
1984	150.6	239.3	104.5	25.4	129.8
1985	125.3	215.4	103.6	14.2	117.3
1986	136.3	220.3	97.2	21.6	118.8
1987/8	116.5	198.1	92.3	30.1	122.4

*Per 1000 births (live and still); †per 1000 live births.
Source: From LHS 27/1; DHSS Statistics and Research, 1987 and 1988.

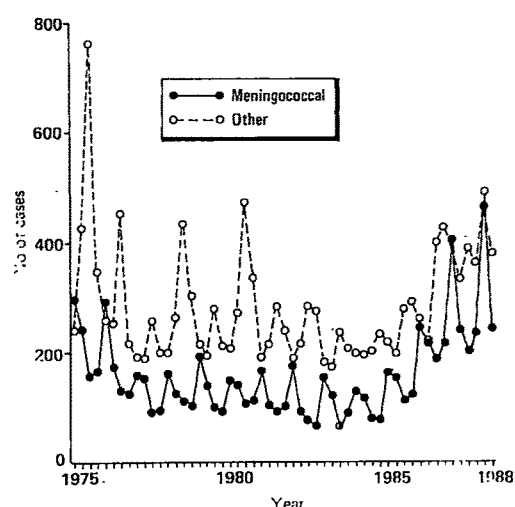
Table 10 Hospital discharge and death rates/10 000 and mean duration of stay (days)

Age (years)	Year						
	1979	1980	1981	1982	1983	1984	1985
0-4							
Discharge and death rate	1308.9	1333.7	1378.1	1405.8	1402.7	1426.8	1500.6
Mean duration of stay	6.3	5.8	5.7	5.4	5.0	4.9	4.8
5-9							
Discharge and death rate	649.9	685.3	702.1	682.4	716.7	716.3	723.2
Mean duration of stay	5.1	4.6	4.4	4.3	4.2	4.4	4.1
10-14							
Discharge and death rate	466.8	491.3	500.5	500.9	523.1	535.1	534.5
Mean duration of stay	6.1	5.7	5.5	5.5	5.1	5.0	4.8

Source: OPCS: Series MB4 No 29, 1989.

1986, however, so that the present situation is that over 50% of these infants now survive the first four weeks.

There are anomalies in the 1987/8 data. The late neonatal mortality for both birthweight groups shows a sharp increase from the previous year. Also the original table published by the Department of Health, and from which table 9 is completed, shows an almost three fold increase in the number of low birthweight infants categorised as 'weight unknown'. This is most likely to be an artifact of the recording system. One possible explanation that would account for both anomalies is a bias in favour of recording the weight of infants that died but not of those that survived. Whatever the explanation it behoves caution in interpreting mortality trends in these groups of infants.



Trends in meningitis notifications. Source: OPCS Monitor Series MB2.

Morbidity

HOSPITAL ADMISSIONS

The admission (more strictly discharge and death) rate of children of all ages to hospital shows a steady upward trend accompanied by a trend towards shorter duration of stay (table 10). Because the data collected are of episodes of illness and not persons, the increasing admission trend could be due to more children being admitted or an increase in the number of admissions per child.

INFECTIOUS DISEASES

The majority (approximately two thirds) of cases of meningococcal meningitis are in children under 15 years of age. The trends in number of notifications of meningococcal and other types of meningitis are shown in the figure. There has been an increase in both groups since about 1984 and it is particularly evident for meningococcal meningitis. The number of cases in the March quarter of 1988 is more than the March quarter of 1974, which was the peak of the last upsurge of this infection.

The increase in the incidence of meningococcal meningitis is a widespread phenomenon with many notifications having been received from several conurbations. Also the epidemic is not confined to a single type of organism—for example, six cases reported from one area were caused by at least three different groups or types.

Immunisation rates continue to be a source of interest and concern. The slow improvement is maintained and is shown in table 11. Attention is drawn to the fact that the 1987 figures are for England only.

Social trends

ONE PARENT FAMILIES

It has long been recognised that children in a one parent family are at risk as shown by several health indices. The one parent family is defined as a mother or father living without a spouse (and not cohabiting) with his/her never married dependent child or children aged either under 16 or from 16 to under 19 and undertaking full time education.² Estimates of the number of one parent families have been obtained from the

Table 11 Percentage vaccination and immunisation of children (Great Britain)

	1971*	1976	1981	1986	1987†
Diphtheria	80	73	82	85	87
Tetanus	80	73	82	85	87
Whooping cough	78	39	46	66	73
Poliomyelitis	80	73	82	85	87
Measles	46	45	54	71	76
Rubella (girls only)			84	87	86

*England and Wales only; †England only.
Source: Social Trends 19, 1989.

General Household and Labour Force Surveys and child benefit statistics. There were just over one million one parent families in 1986 with over 1.6 million dependent children. Since the early 1970s the proportion of all dependent children who live in one parent families has increased by more than 50%, while the proportion of all dependent children who live with a divorced lone mother had trebled.³ These trends have important implications for child health and the provision of a variety of child health services.

PLACE OF SAFETY ORDERS AND CHILD PROTECTION REGISTERS

A child or young person may be removed to a place of safety for varying periods not exceeding 28 days under various statutes. In the year ending March 1987 there were 8400 such orders in England and Wales, an increase of 37% in a decade.

The National Society for the Prevention of Cruelty to Children estimated that 25 700 children's names were added to registers in 1987, of which 8000 were for physical abuse, 7100 for sexual abuse, and 7200 were 'at risk'.⁴

To what extent these numbers quantify the problem is debatable as they will be affected by changing cultural norms, improved awareness, and a variety of other reasons. Nevertheless, these children frequently take up a disproportionate amount of the paediatrician's time and information that sheds light on the magnitude of the problem must surely be welcome.

1 Office of Population Censuses and Surveys. *Occupational mortality, 1979-80, 1982-83*. HMSO, London: 1989. (Childhood Supplement, Series DS No 8.)

2 Department of Health and Social Security. *Report of the committee on one-parent families*. London: HMSO, 1974.

3 Haskey J. One-parent families and their children in Great Britain: numbers and characteristics. *Population Trends* 1989;55:27-33.

4 Central Statistical Office. *Social Trends 19*. London: HMSO, 1989.

PERSONAL PRACTICE

Cystic fibrosis

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The median age at death from cystic fibrosis has increased from six months in 1959 to 17 years in 1986.¹ It is assumed, although proof is lacking, that this improved survival is the result of the liberal use of better antibiotics, closer attention to nutrition and improved pancreatic enzyme supplements, more successful management of meconium ileus, increased ascertainment of milder forms of the disease, and the development of special centres. In the past, incurability was both an attitude of mind and a self fulfilling prophecy, and the notion of early demise insidiously undermined treatment and sapped therapeutic zeal. The greatest change has been a more positive approach. Regrettably, enthusiasm to treat has not been matched by good quality clinical trials, which are hampered by the highly variable nature of the disease, the complexity of clinical scoring systems, and by a system of medical research that encourages short term single centre projects (often carried out by passing registrars whose real interests are not research) when the major need is for longer term multicentre studies of therapeutic approaches. As a result, the modern management of cystic fibrosis remains largely unvalidated. Heated debate about the value of cystic fibrosis centres, the reasons for better survival in certain towns and countries, and the usefulness of neonatal screening are the legacy of poor data. There is a danger that hopes for a cure arising out of research in molecular biology may impede more down to earth objective evaluation of current and future treatment strategies.

Suspecting the diagnosis

Common modes of presentation are described elsewhere.² Unfamiliar presentations are: (i) meconium plug syndrome (most cases do not have cystic fibrosis); (ii) failure to thrive, anorexia, and vomiting accompanied by low serum potassium, chloride and sodium concentrations with a metabolic alkalosis (the biochemical features of pseudo-Bartter's syndrome)—cystic fibrosis may escape early detection in such infants because of an associated low sweat concentration of sodium³; and (iii) failure to thrive with hypoalbuminaemia and anaemia.

Making the diagnosis

The total absence of one or more major features, which are malabsorption due to pancreatic insufficiency, chronic suppurative lung disease, and failure to thrive, make one especially

cautious in the interpretation of the results of sweat tests. Supportive, but not diagnostic evidence are: an abnormal chest radiograph, finger clubbing, the presence of *Staphylococcus aureus* or mucoid *Pseudomonas aeruginosa* in the sputum or a cough swab, an increase in faecal fat excretion, or a sibling with cystic fibrosis. Some patients (less than 10% seen locally, but up to 38% in one Canadian series⁴) have sufficient pancreatic function for normal digestion, so that even the most sophisticated direct pancreatic function testing with triple lumen tube infusion of the duodenum can only exclude pancreatic insufficiency, and not cystic fibrosis itself.⁴ The final diagnosis hinges on the accurate performance and correct interpretation of the sweat test.

The standard procedure in sweat testing is for sweating to be stimulated by pilocarpine iontophoresis to achieve the accurate collection of at least 100 mg of sweat.² Sweat sodium and chloride concentrations are below 40 mmol/l in normal children, and lie between 80 and 125 mmol/l in most children with cystic fibrosis.² Values between 40 and 80 mmol/l are an indication for repeat sweat testing at a cystic fibrosis centre, together with a detailed examination of the clinical features to unravel the cause of the respiratory or gastrointestinal pathology, or both. Other possible conditions associated with raised sweat electrolytes are listed elsewhere.²

Up to 10% of patients with cystic fibrosis referred to regional centres are found to have an alternative diagnosis.^{5,6} The main reasons for these errors are disregard of the clinical features or the lack of them, incorrect performance of the sweat test, and faulty interpretation of the results. Some practical suggestions are:

(i) Ensure that the test is performed by one experienced technician who is familiar with the technique and its problems, the most common errors being loss of sweat by evaporation leading to a falsely high result, and faulty technique causing pain and burns. Delegation to junior staff or medical students is inappropriate. Special caution is required where a hospital performs the test infrequently (that is, less than once a week).

(ii) Measure both sodium and chloride. Discrepancies of more than 20 mmol indicate the need for further testing. The sodium concentration tends to be slightly lower than the chloride in patients with cystic fibrosis, and the reverse in normal subjects. The sum of the sodium and chloride values usually lies above 140 mmol/l. Testing the sodium alone may result in the diagnosis being missed in infancy

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when the sweat may exhibit a high concentration of potassium and normal concentration of sodium.³

(iii) Beware the trap of believing one result in favour of another because it fits with the perceived diagnosis. An example is the patient with a sweat sodium of 51 and 45 mmol/l. A third result was 86 mmol/l and cystic fibrosis was incorrectly diagnosed, disregarding the two previous results not in the range for cystic fibrosis.

(iv) Normal teenagers and adults have higher sweat sodium concentrations than normal children, and 5 to 10% of normal adults have values greater than 60 mmol/l.

Genetics and screening

Referral to the genetic clinic is best made soon after the diagnosis of the first affected child. A calm appraisal of the issues is precluded if a pregnant mother is referred to the genetic clinic as an emergency. Antenatal diagnosis is now possible by analysis of fetal DNA obtained from a chorionic villus biopsy specimen, and in the small proportion of families where this test is uninformative, a less specific test of amniotic fluid for microvillar enzymes can be carried out.

Measurement of the serum immunoreactive trypsin is a useful screening test in the newborn period with only about 1 in 30 000 false negative results, but false positive results (0.3% false positive on first test) mean the diagnosis cannot be made on the results of this test alone.⁷ Screening would abolish late diagnosis, but remains controversial.

Monitoring of patients

Close monitoring of bacterial pathogens in the sputum is a prerequisite for rational antibiotic treatment. Specimens of sputum or throat swabs can be sent by post to the laboratory regularly (for example, every two weeks), enabling the prompt recognition of new pathogens or the emergence of antibiotic resistance.

Visits to the clinic are customarily recommended every six to 12 weeks to monitor the patient's progress, to detect complications or lapses in adherence to treatment, and to continue parent and patient education in the management of the disease. Routine monitoring includes weight, height, lung function tests, occasional checks on the parents' physiotherapy technique, and a six monthly chest radiograph.⁸ An annual abdominal ultrasound examination can be used to detect the development of cirrhosis (untreatable), enlargement of the spleen (also detectable by abdominal palpation) indicating portal hypertension, and gall stones (usually asymptomatic in children). The value of information obtained from ultrasound scans is offset by the annual parental alarm generated by a test that detects largely incurable complications.

Vaccination

There is a special need to ensure that pertussis and measles vaccinations are not delayed (for

example, because the patient has a cough). Influenza can be catastrophic, and there is a case for giving annual influenza vaccination to all patients, giving a half dose to children aged 1 to 3 years (despite the fact that the vaccine is not licensed for use in children under 4 years of age). Deterioration in respiratory function after chicken pox⁹ has led us to use intravenous acyclovir 10 mg/kg/dose, three times daily for five days, starting at the onset of the rash. Eventual exposure is inevitable so there is little point in giving zoster immune globulin after discovery of contact with chicken pox, but it would be helpful if varicella vaccine became freely available. A controlled trial of polyvalent pseudomonas vaccine showed that it failed to prevent pseudomonas colonisation or modify the progress of the disease.¹⁰

Antibiotics

Concern about antibiotic resistance, a lack of objective evidence of efficacy, and high cost have all been used as arguments against the routine use of antibiotics. As one of the main aims of treatment is to prevent lung damage, however, there is no logic in waiting until the patient is coughing up large volumes of purulent sputum or has a high fever. We actively seek respiratory pathogens by frequent sputum culture, and the antibiotic policy is determined by the state of the patient and the pathogens that are isolated.

(i) *Haemophilus influenzae*

As soon as *H influenzae* has been isolated, we prefer to treat with antibiotics (for example, amoxycillin) rather than wait for new symptoms. Amoxycillin resistance necessitates the addition of clavulanic acid or the use of erythromycin.

(ii) *S aureus*

The main aim of giving lifelong oral flucloxacillin is to prevent staphylococcal pneumonia during an intercurrent viral infection. Even with huge doses of flucloxacillin (for example, 3 g four times daily to a 10 year old) combined with fusidic acid (for example, 250 to 500 mg four times a day to a 10 year old), eradication of *S aureus* from the sputum is almost impossible to achieve with antibiotics given orally. Aggressive intravenous regimens using a combination of clindamycin and fusidic acid¹¹ may have a place in the treatment of patients with symptoms in whom *S aureus* is repeatedly recovered from the sputum despite oral antistaphylococcal antibiotics.

(iii) *P aeruginosa*

With the exception of oral ciprofloxacin, the use of which is curtailed by the swift development of permanent resistance, all antipseudomonas antibiotics have to be given by injection (or inhalation). In the past this meant that treatment was confined to acute severe deteriorations with fever. In many units, including ours, this expectant policy has been replaced by a regimen of three monthly courses of intravenous antibiotics for 10 to 14 days in any patient in whom

P. aeruginosa has been recovered from the sputum on more than one or two occasions, regardless of symptoms.¹² It is claimed that such treatment has improved survival,¹³ but this has not been proved.

With careful training of parents, intravenous antibiotics can safely be given at home in many cases, thereby avoiding eight weeks in hospital each year.¹⁴ First line antipseudomonas antibiotics are ceftazidime, semisynthetic penicillins (for example, ticarcillin) and the aminoglycosides (for example, tobramycin, aiming for a serum concentration of 10 to 12 µg/ml, 15 minutes after intravenous injection). Tobramycin is generally given in combination with another agent, and all are given by intermittent injection. Continuous infusion of ceftazidime (75 mg to 300 mg/kg/day) achieves higher and more constant serum concentrations than intermittent injection, a theoretical advantage which merits further study.¹⁵

Microbial resistance to ceftazidime, aminoglycosides, or penicillins is often temporary. Daily sputum sampling during intravenous treatment enables rapid detection of resistance, and a quick change of antibiotic. The increased renal clearance of the penicillins and aminoglycosides in cystic fibrosis, and the need for antibiotics to penetrate pus filled cavities, areas of poor perfusion, and mucopolysaccharide encapsulated strains of *P. aeruginosa*, all require high antibiotic dosage if treatment is to be effective.

P. aeruginosa cannot be eradicated from the sputum of those with advanced bronchiectasis. Frequent sampling of respiratory secretions, however, commonly shows the presence of *P. aeruginosa* in infancy, sometimes before the isolation of *S. aureus* or the development of radiological changes. In such patients it is common to find that the organism becomes impossible to recover from the sputum after one or more courses of intravenous antibiotics. It is reasonable to discontinue regular intravenous antibiotics if pseudomonas has not been recovered for six to 12 months, being prepared to start treatment again if and when the organism reappears.

Inhaled antibiotics, given immediately after physiotherapy, have usually been regarded as second best, and their role is uncertain. It is possible that inhaled antibiotics may diminish frequent relapses requiring intravenous antipseudomonas antibiotics in those with severe lung disease. Drawbacks to the twice daily inhalation of gentamicin 80 mg and carbenicillin 1 g are the time required to administer the drugs by nebuliser, the development of antibiotic resistance, and adverse reactions. A currently popular alternative is colistin,¹⁶ 1 to 2 million units twice daily; the risks of systemic absorption causing renal damage or deafness are unknown but probably small.

(iv) Other strains of pseudomonas

The recovery of *Pseudomonas cepacia* may be associated with a particularly poor prognosis.¹⁷ Response to antibiotic treatment is poor even if the organism is sensitive in the laboratory, and the best hope is that cessation of antipseudomonas

treatment may lead to replacement by *P. aeruginosa*. *P. cepacia* is universally resistant to colistin, and a theoretical worry is that the use of colistin may encourage colonisation by *P. cepacia*. The laboratory will occasionally isolate other strains, such as *Pseudomonas fluorescens*, *maltophilia*, *paucimobilis*, *putida*, or *stutzeri*, but it is not clear whether these are respiratory pathogens.

Bronchodilators and steroids

Wheezing is a common feature of cystic fibrosis. It may be caused by acute infection, in which case antibiotic treatment may help, or it may be due to bronchial hyper-reactivity, a common feature of cystic fibrosis. Response to β_2 stimulants is variable, and there are a number of patients with intermittent or persistent wheezing in whom there is little or no response to inhaled β_2 stimulants, ipratropium bromide, disodium cromoglycate, or inhaled or systemic steroids. The onset of, or increase in, asthmatic symptoms, accompanied by fever, an increased eosinophil count, and the presence of pulmonary infiltrates, suggest the development of allergic bronchopulmonary aspergillosis. Skin prick tests or blood tests for specific IgE antibodies are of little diagnostic value as they are positive in a high proportion of all severely affected patients with cystic fibrosis, but a negative test may be helpful by pointing away from the diagnosis. Some patients respond to bronchodilators alone, but if not then oral steroids are effective.

The use of prednisolone carries a risk of provoking insulin dependent diabetes mellitus, an especially unfortunate complication for an already handicapped patient. Impaired carbohydrate tolerance (seen in up to 40% of patients) leading to insulin dependent diabetes mellitus is seen in 1 to 2% of those with cystic fibrosis under 16, but occurs in up to 7% of adults.¹⁸ The suggestion that prednisone given on alternate days may help lung function in mildly affected patients requires confirmation before it can be recommended.¹⁹

Nutrition

Faecal nutrient losses, poor appetite, respiratory infection, and increased energy expenditure explain why patients require above average energy intakes.²⁰ Low fat diets have now been replaced by diets high in fat, protein, and carbohydrate. The new pH sensitive enteric coated microsphere preparations of pancreatic enzymes Creon (Duphar Laboratories) and Pancrease (Ortho-Cilag) have achieved substantially improved fat absorption, accompanied by diminished abdominal distension, stool odour, and number of bowel actions.²¹ Of the two formulations, Creon has a greater lipase content (8000 units BP per capsule, compared with 5000 units BP in Pancrease)²² and its retail price is lower (£22.99 for 100 capsules, compared with £25.57 in June 1989). The previous goal of fewer bowel actions has been replaced by trying to achieve a normal (5 g/day) faecal fat excretion, and this is usually possible with

between five and 20 capsules of enzyme microspheres/meal. Where enzyme supplements fail to abolish abnormal fat loss in the stool, it can sometimes be achieved with the addition of oral ranitidine twice daily or, failing that, taurine supplements* (500 mg twice daily), the mode of action of which is unclear.²³

Breast milk is usually suitable for infants with cystic fibrosis. For formula fed infants, maximal intake of nutrients with a minimal need for pancreatic supplements can be achieved with a casein hydrolysate milk formula to which is added a fat emulsion and additional carbohydrate (appendix 1). For older patients who stop gaining weight and have poor appetites, weight gain can sometimes be achieved by giving nutritional supplements based on skimmed milk powder; examples are Complan (Farley) or Build-Up (Carnation). Suitable carbohydrate supplements are Maxijul (Scientific Hospital Supplies), Caloreen (Roussel), or Polycal (Cow and Gate) and a suitable medium chain triglyceride supplement is Liquigen (Scientific Hospital Supplies). Finally there are flavoured food supplements, for example, Fresubin (Fresenius) or Fortisip (Cow and Gate). Short or long term nocturnal enteric feeding with a peptide based feed (appendix 2), occasionally causes remarkable benefit to general health but can also be an intolerable burden, and the indications for such treatment have yet to be established.²⁰ Where nocturnal feeding is successful and is planned for long term use, the need for a nasogastric tube can be avoided by the simple procedure of an incisionless gastrostomy.²⁴

Although it is common practice to give multivitamin supplements such as Ketovite (Paines and Byrne), and fluoride tablets where the tap water has a low fluoride content, the need for water soluble vitamins is doubtful.²⁰ The need for supplements of fat soluble vitamins is uncertain. Asymptomatic conjunctival xerosis, possibly the result of vitamin A deficiency, has recently been reported in three children with cystic fibrosis, and this is a topic that merits further study.²⁵

Severe deficiencies of vitamin D and K are rare in cystic fibrosis. Vitamin E deficiency causing haemolytic anaemia and only partly reversible spinocerebellar degeneration and peripheral neuropathy is a rare complication of cystic fibrosis, found particularly in patients with liver disease or who have had ileal resection. The risk of vitamin E deficiency merits the routine use of vitamin E supplements in a dose of 45 mg to 200 mg/day. The optimum dose and the role for monitoring serum concentrations are uncertain.

Physiotherapy

A zealous commitment to chest physiotherapy is a universal feature of treatment, but practices vary more than any other aspect of cystic fibrosis management. In Britain physiotherapy

is based on percussion, postural drainage, and the forced expiratory technique (huffing), whereas in many European countries patients are trained to perform the Belgian or German forms of 'autogenic drainage' in which a form of controlled breathing is supplemented by the use of inhalations of moisture, breathing against a positive expiratory pressure, and the forced expiratory technique.²⁶ The advantages of the latter approach comprise patient independence (percussion is eschewed) and greater flexibility tailored to the needs of the patient, but as with all forms of physiotherapy there is need for objective evaluation. It is not clear whether daily and prolonged (30 minutes or more) running or cycling can replace physiotherapy, but the clinical benefits to patients sufficiently committed to vigorous exercise can be impressive.

Complications

Pneumothorax affects up to 20% of teenagers and adults with cystic fibrosis. Recurrences are common, and may require chemical pleurodesis or pleurectomy, though the resulting adhesions may prevent subsequent heart-lung transplantation.²⁷ Mild haemoptysis is common and responds to antibiotic treatment of the underlying chest infection. More severe episodes warrant the exclusion of coagulation defects resulting from liver disease or hypersplenism, and may stop only after blood transfusion and bronchial artery embolisation. Alveolar hypoventilation may lead to hypoxic pulmonary hypertension and cor pulmonale, which has a poor prognosis. Digoxin is no use, but diuretics are of some value for cardiac failure.

Gall stones or sludge in the gall bladder are detectable in up to 10% of children with cystic fibrosis but are asymptomatic, and cholecystitis and biliary colic are mainly confined to those over 16 years of age. Ten to 25% of children develop bile duct obstruction with abnormal mucus, and possibly also stenosis of the common bile duct causing focal biliary fibrosis, the precursor to the development of cirrhosis which affects about 5% of patients by adult life.²⁸ The main complications of cirrhosis are bleeding oesophageal varices and hypersplenism. The standard advice has been to ignore varices until they bleed. The exception is in the patient with varices and thrombocytopenia caused by hypersplenism in whom the first variceal bleed is likely to be fatal, and there may be a case for splenic embolisation in such patients.

Meconium ileus equivalent has almost disappeared with the use of pancreatic enzyme microspheres, and nowadays seems to be mainly associated with insufficient doses of enzymes. The features are colicky abdominal pain, and a faecal mass in the right iliac fossa, plus constipation and sometimes intestinal obstruction. After appendicitis and intussusception have been excluded, mild cases can be treated with oral N-acetylcysteine (for example, 10 ml four times a day) or one or two doses of oral Gastrografin (50 to 100 ml, taken with 200 to 400 ml of water). Those with obstruction require intravenous

*Taurine capsules are made by Istituto Farmochimico Nativelle SPA, Firenze, Italy, and obtainable in the United Kingdom from Idis Ltd, 51 High Street, Kingston upon Thames, Surrey, KT1 1LD, tel 01-549-1355.

fluids, N-acetylcysteine or Gastrografin enemas, and occasionally operation.

Asymptomatic radiological opacity of the paranasal sinuses and underdevelopment of the frontal sinuses are almost universal in cystic fibrosis. Nasal polyps, present in 6% to 36% of patients, may cause nasal obstruction and distortion, but many patients have no symptoms and spontaneous resolution is well described. Operation is commonly followed by recurrence, and is best confined to those with troublesome symptoms who have failed to respond to steroid nose drops.

Arthritis beginning in the teens is seen in about 10% of young adults with cystic fibrosis. In about half this is caused by hypertrophic pulmonary osteoarthropathy, with radiological changes of periostitis in long bones, exacerbations during chest infections, a mean age of onset of 15 years, and only an initial response to non-steroidal anti-inflammatory drugs. In most of the remainder the symptoms are the result of episodic arthritis with painful joint swelling, stiffness (often accompanied by fever and erythema nodosum), and a mean age of onset of 11 years. The attacks last no more than four days and generally respond well to non-steroidal anti-inflammatory drugs.

The fatal outcome, male sterility, delayed sexual development, chronic ill health, the need for life long treatment, a desire for independence, and the genetic aetiology all contribute to the impressive social and psychiatric toll of this disease; this includes teenage rebellion, non-compliance with treatment, marital breakdown, and parental psychiatric disorder. Sensitive ward staff, liaison nurses, and social workers are the key to detecting problems that can otherwise be concealed for years.

A diminishing response to intravenous antibiotics in a child with advanced lung damage, or the onset of cardiac failure, are signs of a poor prognosis. It makes no sense to subject a child near death to the misery of futile and unpleasant treatment. Most families prefer terminal care at home. Oxygen helps to relieve dyspnoea, and may help the child to tolerate physiotherapy. Carbon dioxide narcosis cannot be relied upon to occur, and there should be no hesitation in giving opiates to distressed terminal patients. Heart-lung transplantation offers hope for a small number of patients for whom donor organs are available, but generates false optimism and disappointment for most.²⁷

The place of regional centres

Families sufficiently motivated to travel enormous distances to a regional centre cannot possibly be compared with those who require cajoling to attend a local hospital. The case for special centres in the United Kingdom is not strengthened by claims that do not allow for this fact.²⁹ Parents increasingly demand treatment in special centres, which are likely to have better laboratory and paramedical facilities (physiotherapy, dietetics), wards better geared to the needs of the patients, support from other children with cystic fibrosis and their parents, and a team approach. It is difficult for those

who see only the occasional case to provide up to date treatment without the backup of the facilities of a cystic fibrosis centre. The logical solution at present is for care at cystic fibrosis centres for those patients living nearby, or those wishing to travel. For the rest some sort of shared care is desirable. A challenge for paediatricians is to find adult chest physicians who are prepared to take a special interest in young adults with cystic fibrosis.

Conclusions

Whatever the reason, modern management has brought far longer survival and improved health during childhood. The price for survival into adult life is a considerable amount of medical intervention that impinges on the life of the patient and family. Many parents hope for a cure, but improvements in antibiotic and nutritional management are more realistic short term hopes.

Much of the current treatment of cystic fibrosis is based on dogma masquerading as science. Single centre studies cannot answer important therapeutic questions, such as the value of antipseudomonal or antistaphylococcal regimens. The energy devoted to endless arguments about whether patients ought to attend special centres would be better used to initiate a nationally coordinated multicentre study of specific therapeutic regimens. Highly successful precedents for this approach exist in the Medical Research Council trials of leukaemia treatment, and the United Kingdom Children's Cancer Study Group trials of solid tumour treatment.

Appendices

Appendix 1: Infant milk formula for cystic fibrosis: Pregestimil (Mead Johnson) 100 ml, to which is added 5 ml Liguigen (Scientific Hospital Supplies) and one Pregestimil scoop (3.4 g) of Maxijul (Scientific Hospital Supplies). This provides approximately 1 kcal/ml (0.0042 MJ/ml).

Appendix 2: Enteral feeding regimen: Pepti 2000 LF (Cow and Gate), containing short chain peptides (thus avoiding the need for pancreatic enzymes), maltodextrin, corn oil, medium chain triglyceride, vitamins and minerals, approximately 1 kcal/ml (0.0042 MJ/ml). Start with one sachet (126 g) dissolved in 500 ml water, and give by a Fortison Enteral Pump through a fine bore nasogastric tube; which is passed each bedtime. Either one can increase the volume as much as possible (limited by vomiting or nocturia) and then increase the concentration of the solution as much as possible, or one can aim to give a specific amount (for example, 30% of the recommended daily amount for energy).

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LETTERS TO THE EDITOR

Research in community child health

SIR,—Dr Polnay's annotation is to be applauded and if his research agenda emphasises operational aspects this befits a speciality where new and old practices need rigorous evaluation.¹ Epidemiology as a research skill deserves further comment. Community paediatricians are peculiarly well placed to use epidemiological techniques in studies of practice and disease. Having a service role in the community they already know their population and are well accepted by public and colleagues alike. Hence it is to be regretted that while there is considerable research into child health in the community this is conducted by educationalists, sociologists, *et al*, rather than community paediatricians.

Being the basic science of public health some understanding of epidemiology is needed by any community paediatrician looking beyond individual patients and a district service is strengthened if an established post carries a deeper knowledge of the subject. However acquiring appropriate training is difficult. Courses are dominated by adult medicine and a children's doctor may be fed an indigestible diet of cardiovascular and cancer epidemiology. The paediatric courses at the Institute of Child Health are an unusual exception and similar training should be offered elsewhere. However, as Dr Polnay notes, the limiting factor is a famine in training funds for children's doctors and at the core of this is ambivalence over their role in the rediscovered speciality of public health. It is unfortunate that the substantial forces of community paediatrics were ignored by those planning the future,² and the allocation of training funds will probably reflect this myopia. I would suggest that one way out of the impasse is for community paediatrics to recreate links (joint posts, joint research) with departments and units of community/public health. It should be possible to do so from a position of strength within broader paediatrics and indeed such initiatives have started from some academic institutions. Hence Dr Polnay is doubly correct to regret that not all departments of child health have taken up the challenge of community work.

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2 Committee of Inquiry Into the Future Development of the Public Health Function. *Public Health in England*. London: HMSO, 1988.

Screening infants for hearing loss

SIR,—Brown *et al* have critically evaluated the distraction hearing test as a screening pro-

cedure.¹ Their results are similar to those obtained from a smaller survey conducted over a one year period in Litherland, a predominantly working class district of South Sefton area health authority, Merseyside.

Over the year period 1986-7, 261 children, or 68% of the target population, were screened. Of those who were screened eight children, or 3%, failed a second test and were referred to the audiology clinic. Five of the eight children were confirmed as having a moderate severe conductive hearing loss; the three remaining children were considered to have normal hearing. One child was treated with myringotomies and grommets, and the remainder were eventually discharged from the ear, nose, and throat clinic. It was estimated that approximately 240 hours of health visitor time were spent in performing the test, persuading defaulters to attend, and in administration.

Brown *et al* found that attendance for the test varied with immunisation record. In Litherland 41% of non-attenders completed a primary immunisation course compared with 71% of those who attended for the distraction test. Only 52% of non-attenders had both developmental checks, at 6 weeks and 6 months of age, compared with 81% of attenders.

The technique of the four health visitors who performed the tests was examined. It was found that the testing technique was overall satisfactory but that minimal distraction levels were not always possible due to ambient noise in clinic premises. The usefulness of the distraction test as a means of detecting sensorineural deafness must be questioned. In Litherland one significant case of conductive deafness was identified at the expense of six weeks of health visitor time. Newton has suggested that at best only 50% of cases of sensorineural deafness will be identified at 8 months by means of the distraction test and that those deaf children who 'pass' the test are detected at a significantly later age.² Early detection of nerve deafness is highly desirable; however, the distraction test appears to be of limited use in achieving this aim.

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1 Brown J, Watson E, Alberman E. Screening infants for hearing loss. *Arch Dis Child* 1989; 64:1488-95.

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Acquired transient protein C deficiency in neonatal cardiac failure

SIR,—Protein C is a vitamin K dependent plasma protein of hepatic origin. Activated protein C inhibits coagulation factors Va and VIIIa and stimulates fibrinolysis. Hereditary protein C deficiency has been widely described. Heterozygotes with protein C activity concentrations of around 50% normal are at increased risk of venous thromboembolism.¹ Homozygotes with protein C concentrations of less than 5% normal may present in the neonatal period with purpura fulminans² or inferior vena caval thrombosis.³ Acquired protein C deficiency has been described in

liver disease, disseminated intravascular coagulation, adult respiratory distress syndrome, and in the postoperative period.⁴

Two infants born at this hospital suffered a severe non-hereditary neonatal protein C deficiency in association with cardiac failure due to a supraventricular tachycardia.

The first infant was born at 34 weeks' gestation, by emergency caesarean section for fetal distress. At birth the baby boy was noted to have a blue/white pulseless right arm, further examination showed a supraventricular tachycardia, tachypnoea, and hepatomegaly. Treatment with digoxin, frusemide, and heparin corrected the supraventricular tachycardia and cardiac failure, and the pulses gradually returned to the right arm with reperfusion. Initial protein C activity was <5%; after treatment with vitamin K and correction of the cardiac failure the activity rose to 25% at two weeks and subsequently to 79% at 15 months. Both parents have normal protein C activity.

The second infant was born at 38 weeks, gestation by vaginal delivery. At birth he was grossly hydropic with hepatomegaly, oedema, and noticeable ascites. He also had a supraventricular tachycardia and in addition a widespread purpuric rash. His platelet count was normal and screening for intrauterine viral infections was negative. His protein C activity was also <5% and improved rapidly to 30% activity by the age of 1 week and 45% by 2.5 weeks with vitamin K treatment and correction of cardiac failure. His parents also had fully normal activity.

Both of these babies showed transient severe reduction in protein C activity in association with neonatal cardiac failure; neither is homozygous for hereditary protein C deficiency and none of the parents is heterozygote. Both infants developed neonatal jaundice requiring phototherapy and both had further evidence of vitamin K deficiency with prolonged prothrombin time and reduced factor II (5% and 3% respectively). Neither infant had evidence of disseminated intravascular coagulation.

We suggest that cardiac failure in the neonatal period (when liver function is poor and vitamin K deficiency may coexist) can impair hepatic production of protein C with consequent risk of thrombotic complications. If this is shown to be the case it will have significant implications for the management of infants with major congenital heart disease, especially those undergoing neonatal surgery or invasive investigations. To our knowledge no one has systematically investigated protein C concentrations in severe neonatal heart failure.

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1 Broekmans AW, Veltkamp JJ, Bertina RM. Congenital protein C deficiency and venous thromboembolism. A study of three Dutch families. *N Engl J Med* 1983;309:340-4.

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Pressure flow characteristics of the valve in spacer devices

SIR,—The 'drug delivery from a holding chamber with facemask to infants will be dependent upon many factors including chamber size, aerosol density, dead space from valve to patient, and efficiency of valve. The paper by Sennhauser and Sly is an attempt to look at one of these parameters.¹ Our visual observation would agree with theirs: that the Volumatic valve (Allen and Hanburys) will close at lower flow rates than that of the Nebuhaler (Astra). However, the purpose of such a device is to deliver drug to the infant and we find consistently more drug is delivered from the Nebuhaler than the Volumatic, even at low flow rates (unpublished results).

It is our belief that neither valve is ideal for use in young infants and more efficient valves are required. An attempt has been made to adapt the Nebuhaler valve to the requirements of infants,² but this increases its complexity and dead space.

At present we use Nebuhaler and facemask to deliver drugs such as steroids and ipratropium bromide. After actuation of the metered dose inhaler the Nebuhaler is tilted, opening the valve, which then remains open. As the device is only applied for 10 seconds any effects from rebreathing are small and very transient.

Although we believe that such devices will prove to be a useful addition to our present repertoire we require further information not only on design features required to maximise drug delivery but also on the role of various drugs delivered by this route to infants.

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¹ Sennhauser FH, Sly PD. Pressure flow characteristics of the valve in spacer devices. *Arch Dis Child* 1989;64:1305-7.

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MEETINGS IN 1990

Ambulatory Pediatric Association

7-11 May, Anaheim, California

Further details: Dr Marge Degnon, 6728 Old McLean Village, McLean, VA 22101, USA

American Pediatric Society

7-11 May, Anaheim, California

Further details: Ms Debbie Anagnostellis, Society for Pediatric Research, 2650 Yale SE, Suite 104, Albuquerque, New Mexico 87106, USA

British Association of Perinatal Medicine

15 September, University of Wales College of Medicine

Further details: Dr Mark R Drayton, University Hospital of Wales, Department of Child Health, Heath Park, Cardiff CF4 4XN

British Paediatric Association

3-6 April, University of Warwick

Further details: Miss RJ Topping, British Paediatric Association, 5 St Andrew's Place, Regents Park, London NW1 4LB

British Paediatric Respiratory Group

5-6 October, Joint Meeting with the Dutch Respiratory Group, The Hague, The Netherlands

Further details: Dr Warren Lenney, Royal Alexandra Hospital for Sick Children, Dyke Road, Brighton, East Sussex BN1 3JN

Clinical Genetics Society

18-20 April, University of Newcastle upon Tyne

Further details: Dr John Burn, Human Genetics Department, 19 Claremont Place, Newcastle upon Tyne NE2 4AA

European Society for Paediatric Endocrinology

2-5 September, Vienna

Further details: Dr H Frisch, Department of Endocrinology, University Children's Hospital of Vienna, Wahringer Gurtel 18-20, A-1090 Vienna, Austria

European Society of Paediatric Gastroenterology and Nutrition

25-27 May, Amsterdam

Further details: Dr A Dowes, Free University Hospital, Amsterdam Children's Department, PO Box 7057, NL-1007, Amsterdam, The Netherlands

European Society for Paediatric Nephrology

30 September-4 October, Rome

Further details: Dr Michael Winterborn, Paediatric Dialysis Unit, East Birmingham Hospital, Bordesley Green East, Birmingham B9 5ST

European Society for Pediatric Research

23-27 September, Vienna

Further details: Professor K Widhalm, Department of Pediatrics, University of Vienna, Wahringer Gurtel 18-20, A-1090 Vienna, Austria

International Congress on Child Abuse and Neglect

2-6 September, Hamburg

Further details: PO Box 30-24-80 D-200, Hamburg 36, Federal Republic of Germany

The Neonatal Society

1 March, Royal Society of Medicine, London

13-15 July, St John's College, Cambridge
Further details: Dr Caroline Beardsmore, Department of Child Health, Clinical Sciences Building, Leicester Royal Infirmary, PO Box 65, Leicester LE2 7LX

Paediatric Research Society

30-31 March, Edinburgh

Further details: Dr John Osborne, Royal United Hospital, Combe Park, Bath BA1 3NG

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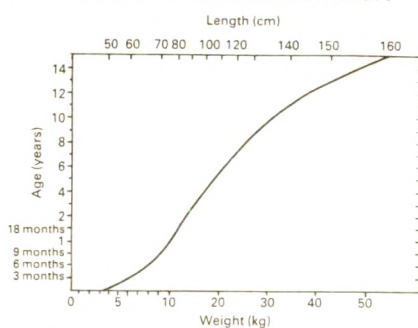
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12	4.0
11	3.5
10	3.0-3.5

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Calcium chloride (mmol)* intravenous	1	2	4	6	8	10
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ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the British Paediatric Association

Annotation

- 161 Do chesty children become chesty adults? *D P Strachan*

Original articles

- 163 Survey of asthma deaths in the Northern region, 1970–85 *H J Fletcher, S A Ibrahim, N Speight*
- 168 Estimation of lung volume in infants by echo planar imaging and total body plethysmography *B Chapman, C O'Callaghan, R Coxon, et al*
- 171 Airway function in infants with vascular rings: preoperative and postoperative assessment *A H Thomson, C S Beardsmore, R Firmin, et al*
- 175 Bacterial reservoirs in cystic fibrosis *C J Taylor, J McGaw, R Howden, et al*
- 178 Ontogeny of pancreatic exocrine function *S Kolacek, J W L Puntis, D R Lloyd, et al*
- 182 Submucous cleft palate in the differential diagnosis of feeding difficulties *A L H Moss, K Jones, R W Pigott*
- 185 Factors influencing the presence of faecal lactobacilli in early infancy *M A Hall, C B Cole, S L Smith, et al*
- 189 *Helicobacter pylori* in Gambian children with chronic diarrhoea and malnutrition *P B Sullivan, J E Thomas, D G D Wight, et al*
- 192 Understanding non-attendance in outpatient paediatric clinics *R Andrews, J D Morgan, D P Addy, et al*
- 196 Pharmacokinetics of prednisolone in children with nephrosis *P F W Miller, C J Bowmer, J Wheeldon, et al*
- 201 Cerebral palsy in very low birthweight infants *R W I Cooke*
- 207 Neonatal pneumonia *S Webber, A R Wilkinson, D Lindsell, et al*
- 212 Prognosis of Down's syndrome with acute leukaemia *G A Levitt, C A Stiller, J M Chessells*
- 217 Who's in CHARGE? Multidisciplinary management of patients with CHARGE association *K D Blake, I M Russell-Eggitt, D W Morgan, et al*
- 224 Iron in tubewell water and linear growth in rural Bangladesh *A Briend, B A Hoque, K M A Aziz*
- 225 The five year school medical—time for change *G C Smith, A Powell, K Reynolds, et al*
- 227 Isolated fructose malabsorption *J K H Wales, R A Primhak, J Rattenbury, et al*
- 229 Dietary management of D-lactic acidosis in short bowel syndrome *A J Mayne, D J Handy, M A Preece, et al*
- 231 Atopic eczema, hyponatraemia, and hypoalbuminaemia *H M Goodyear, J I Harper*
- 232 Growth failure secondary to moyamoya syndrome *C A MacKenzie, R D G Milner, U Bergvall, et al*
- 234 *Staphylococcus epidermidis* and retention of neonatal percutaneous central venous catheters *G Gladman, S Sinha, D G Sims, et al*
- 236 Cryptosporidiosis and acute leukaemia *A B M Foot, A Oakhill, M G Mott*

Current topic

- 238 Monitoring and sudden infant death syndrome: an update *Report from the Foundation for the Study of Infant Deaths and the British Paediatric Respiratory Group*

Personal practice

- 241 Management of acute upper airway obstruction in an intensive care unit in a district general hospital *G H Lear, S A McKenzie, H Boralessa*
- 246 Neonatology—then and now *C H M Walker*
- 247 Letters to the editor

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ARCHIVES OF DISEASE IN CHILDHOOD

Annotation

Do chesty children become chesty adults?

The possible links between experiences in childhood and disease in adult life have become topical in recent years.¹ The suggestion that chest illness in childhood may contribute to the development of chronic respiratory problems in middle and old age, however, has intrigued researchers for at least two decades.² Two chronic respiratory conditions of childhood, asthma and bronchiectasis, provide rather different models for such a link between childhood and adult disease.

Childhood asthma, adult asthma, and chronic airflow obstruction

Few studies provide prospective information on the long term prognosis of childhood asthma. Blair followed up 267 children who had attended his east London general practice with asthma under 12 years of age.³ Twenty years later, one half had mild or no asthmatic symptoms but 21% had remained symptomatic throughout adolescence, and a further 27% had relapsed after at least three years free of symptoms. Relapse often occurred in the late teens, highlighting the problems of determining prognosis from many of the earlier clinical series with shorter periods of follow up.³

Population based data are provided by the ongoing follow up of British births during one week in 1958.⁴ Among 1899 children with a history of asthma or wheezy bronchitis ascertained at 7 years of age, 10% reported asthma or wheezy bronchitis in the past year at 23, and a further 10% recalled an attack since their 16th birthday. These figures compare with 3% and 4%, respectively, for 8658 subjects with no history of wheezing illness in early childhood.

The most comprehensive information on the natural history of childhood asthma is provided by the follow up of 323 wheezy children in Melbourne, Australia, who were most recently examined at 28 years of age.⁵ Three quarters of the wheezy children identified in the population at 7 years of age had ceased to wheeze by age 14. Nearly half of this group reported wheeze in the past three years at age 28 years, but less than 10% had attacks more than once a week. Two thirds of the 47 children with frequent or unremitting childhood asthma (often associated with an early onset) continued to have attacks of wheeze more than once a week at age 28, and only one had become asymptomatic. The outcome among children with less frequent attacks at age 14 was intermediate: over 80% continued to wheeze, but only one third had weekly attacks. Symptoms had worsened in

over one third of those with no or infrequent wheezing at 21 years of age.

Together, these studies confirm that some wheezy children continue to wheeze as young adults, although the proportion that 'grow out' of their asthma differs considerably between studies, probably due to different methods of identifying wheezing attacks. The tendency for symptoms to relapse after periods of partial or complete remission emphasises the chronic nature of the condition. What is unknown is how an active or latent wheezing tendency in the 20s relates to asthma and chronic airflow limitation in middle and old age.

There is some evidence that a diagnosis of asthma,^{6,7} or non-specific bronchial reactivity,^{8,9} are risk factors for more rapid decline of ventilatory function in middle age, but the interpretation of such findings is complex. Both bronchial reactivity and rapid functional decline are associated with low initial values for spirometric indices, and the cause-effect relationships among these three features are unclear. Other data suggest that adult asthmatics do not have accelerated rates of lung function decline.¹⁰

Lower respiratory tract infection, chronic bronchitis, and emphysema

Although bronchiectasis is declining as a clinical and public health problem,¹¹ its onset after severe episodes of pneumonia, even in the previously healthy child, provides a basis for the concept that frequent lower respiratory tract infections in early childhood might result in subclinical damage to the lung that later manifests itself in chronic phlegm production and, perhaps, airways obstruction. It has been pointed out, however,¹² that 'lung damage' due to childhood chest illness does not readily fit with current concepts of the pathogenesis of pulmonary emphysema, which is probably the major determinant of chronic airflow limitation and mortality from chronic respiratory disease in middle age.

The suggestion that chronic bronchitis might have its origins in childhood was originally prompted by epidemiological observations that respiratory mortality and morbidity in both childhood and adult life showed similar variations between countries, regions of Britain, urban and rural areas, and socioeconomic groups.² More recently, a striking geographical correlation has been described between respiratory mortality among infants during 1921-5, and adult mortality attributed to chronic bronchitis during 1968-78 in England and Wales.¹³ Few studies have addressed the effect

of migration between low and high risk areas, which would clarify the relevance of the geographical patterns to the 'childhood origins' hypothesis. National servicemen recruited from industrial areas carried an increased risk of admission for respiratory disease, however, regardless of the region to which they were posted.¹⁴

At the individual level, both retrospective and prospective studies support a link between childhood chest illness and respiratory problems in adults. There has been little new evidence published since the subject was comprehensively reviewed in 1983.¹² The longest established prospective study is based upon the British 1946 birth cohort.^{15,16} The association between chronic winter cough and a history of bronchitis or pneumonia in early childhood, which had been found at ages 20 and 25, was confirmed at 36 years of age. After adjustment for smoking, housing tenure, and domestic crowding in childhood, the prevalence of winter cough among 828 children with a history of respiratory illness by age 10 was 10.5%, compared with 7.4% among the 2254 with no such history.¹⁵ The corresponding mean adjusted peak expiratory flow rates (PEFR) were 475 l/min and 485 l/min. Mean adjusted PEFR was also lower among the 1695 children with a history of whooping cough by age 10, but chronic cough was less common in this group.¹⁶

The nature of the childhood illnesses labelled as 'bronchitis' in this and other studies is unclear, and many may have been related to asthma.¹⁷ In both the Melbourne study¹⁸ and the British 1958 cohort,⁴ adults in their 20s who recalled recent attacks of asthma or wheeze also appeared to be at considerably increased risk of chronic cough and phlegm production, among both smokers and non-smokers. In the 1958 cohort, the association between chest illness in childhood and chronic cough or phlegm at age 23 was almost entirely attributable to persistence of a wheezing tendency.⁴ Ventilatory function tests have not yet been performed in this cohort, but as wheezy young adults have lower mean levels of forced expiratory volume in one second⁵ and PEFR,¹⁵ it seems likely that at least part of the association between childhood chest illness and reduced levels of ventilatory function in adults^{6,15,19} may be related to the chronic manifestations of asthma.

Studies relying upon retrospective ascertainment of childhood disease must be interpreted with caution, but it is pertinent to note that in one, the respiratory problems in childhood which were associated with adult obstructive airways disease were those in the category of 'chronic or recurrent airway disease', rather than 'severe acute respiratory illness'.¹⁹ The former group had a more adverse outcome, however, even when those with a diagnosis of asthma in childhood or adulthood were excluded from the analysis.¹⁹

Conclusion

Clearly, much remains to be clarified about the natural history of asthma and its associations with other respiratory disorders in children and adults, but potentially it could have a central role in explaining continuities of respiratory morbidity between childhood and later life. The suggestion that acute lower respiratory tract infections in childhood may be a cause of airways obstruction in adulthood remains one of the most intriguing and elusive epidemiological hypotheses spanning, as it does, from infancy to late middle age, and from one poorly defined disease category to another.²⁰ Nevertheless, its solution may be of considerable importance in evaluating the public health burden posed by the extremely common, but often self limiting, respiratory illnesses of early childhood.

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ORIGINAL ARTICLES

Survey of asthma deaths in the Northern region, 1970-85

H J Fletcher, S A Ibrahim, N Speight

Abstract

Thirty five asthma deaths in children aged 1 to 16 years were investigated in detail. Twenty four of these children had previously been under hospital consultant care and there were seven inpatient deaths. Twenty nine cases (83%) had a history of severe asthma, 17 of whom had previously experienced a life threatening attack. The fatal outcome, however, could not have been predicted in six children (17%) with preceding mild asthma. Potentially preventable factors in management were found in 28 cases (80%). While 18 (51%) had been chronically undertreated, the major factor in 20 deaths (57%) was suboptimal management of the final attack owing to delay in seeking medical attention, inadequate medical response, or both. Only two children had received systemic corticosteroid in appropriate amounts during the final illness.

If mortality is to be reduced, families of asthmatic children must be educated to recognise severe symptoms and be given an appropriate 'crisis plan'. Hospitals should permit free access and have a clear protocol for the management of children with severe asthmatic attacks.

Asthma affects approximately 10% of the childhood population. It carries a small mortality which, despite therapeutic advances during the past two decades, has not declined significantly. Studies in adult asthmatics have shown repeatedly that around 80% of deaths occurred as a result of poor patient education, supervision, and management.^{1 2} A recent New Zealand survey on childhood asthma deaths suggested that they were largely preventable.³ In this country, similar conclusions were drawn by Carswell in his review of 30 childhood asthma deaths.⁴ More than half of the children he studied died before 1970, however, and the detailed circumstances of many of the deaths were not investigated. This study of childhood asthma deaths in the Northern region explores whether such deaths were predictable or preventable.

Subjects and methods

Names of children aged 1 to 16 years inclusive, who were certified as having died of asthma in the period between January 1970 and December 1985, were obtained from the Office of Popula-

tion Censuses and Surveys (OPCS). All had resided in the area covered by the Northern health region, which includes the counties of Northumberland, Cumbria, Durham, Cleveland, and Tyne and Wear.

Permission was obtained for hospital case notes, coroner's reports, and where possible family practice, school health, and school attendance records to be made available. These were examined in detail. The diagnosis of asthma as a cause of death was based either on a convincing clinical history or findings at post-mortem examination. With the approval of the current general practitioner, parents of the deceased children were contacted by letter and those who agreed to participate in the study were interviewed at home (by SAI or HJF). The interviews were conducted between 1985 and 1987. The time between date of death and date of interview ranged from one to 15 years with a median time of seven years.

All the information was then reviewed with particular reference to the following aspects: (i) whether asthma had been diagnosed before death; (ii) education received by families regarding the disease and its management; (iii) detailed circumstances of the final illness; and (iv) the adequacy of the medical management both before and during the final attack (assessed according to accepted standard treatment at the time).

The study was approved by the relevant district ethical committees.

Forty six recorded asthma deaths were obtained from OPCS of which three were found on further investigation to have died from other causes. One death was reported to us from another source. There were therefore 44 asthma deaths. Postmortem reports were available for 29 of these.

The distribution of deaths over the study period is shown in table 1. During this period, the average annual mortality rate for asthma for children aged 1 to 14 years in the Northern region was calculated to be 0.34/100 000. This was slightly less than the equivalent figure for England and Wales (0.44/100 000) calculated from OPCS data.^{5 6}

The age and sex distribution is shown in table 2. Deaths occurred predominantly in the preschool and adolescent age groups, which was consistent with national data.^{5 6}

Time of death was evenly distributed over 24 hours. Half the deaths occurred in the months of June to September. Twenty eight of the 44

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Table 1 Number of recorded deaths in each year of study (n=44)

	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985
No of deaths																
(No investigated)	4 (2)	6 (3)	1 (0)	2 (2)	1 (1)	2 (2)	1 (1)	2 (2)	1 (1)	3 (2)	2 (1)	3 (3)	2 (2)	8 (7)	5 (5)	1 (1)

Table 2 Age and sex distribution of recorded asthma deaths

Age (years)	Boys	Girls	Total
1-4	3	11	14
5-8	1	3	4
9-12	2	4	6
13-16	12	8	20
Total	18	26	44

children died during a weekend (between 6 pm on Friday and 8 am on Monday). Twenty seven deaths occurred at home or elsewhere, five in transit to hospital, and 12 in hospital.

Parents were interviewed in 30 cases. Sufficient information was available from other sources to include five further cases, so that 35 of the 44 deaths were investigated in detail. The nine remaining cases were not investigated because general practitioners considered it inappropriate to contact the families, parents declined to be interviewed, or could not be traced. Most of these had died in the early part of the study period.

Results

PREVIOUS PATTERN AND SEVERITY OF ASTHMA
Twenty four children had developed their first symptoms of asthma before the age of 3 years. Cases were grouped according to the frequency of symptoms during the two years before the final episode as shown in fig 1.

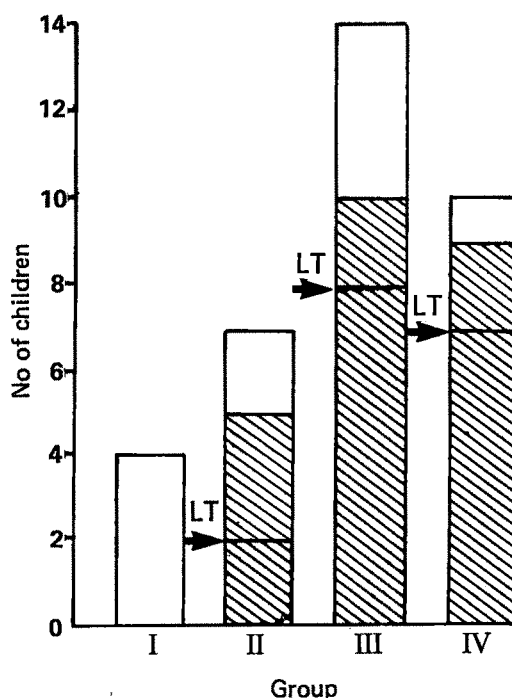


Figure 1 Frequency and severity of wheezing episodes during last two years of life. Group I, <4 episodes of wheeze/year; group II, 5 to 12 episodes of wheeze/year; group III, >12 episodes of wheeze/year; and group IV, permanent wheezing. Hatched area represents children experiencing ≥1 severe episode requiring emergency treatment. LT indicates the number of children experiencing ≥1 life threatening attack.

Severity of the worst previous attack

Twenty four of the 35 children had within the last two years suffered one or more severe attacks that had warranted emergency administration of one or more of the following treatments: intravenous, subcutaneous, or nebulised bronchodilator, and intravenous corticosteroid or oxygen, or both. Seventeen of these cases had suffered one or more life threatening episodes, associated with at least one of the following features: prolonged cyanosis, 'silent chest', pulsus paradoxus, loss of consciousness, cardiorespiratory arrest or documented hypercapnia. These signs were well documented in the hospital case notes of 13 cases and were described by parents or the general practitioner in the remaining four.

Overall severity

Symptom frequency was not always related to the overall severity of the condition. Taking all factors into consideration, the four cases assigned to group I and two of the seven cases in group II appeared to have had relatively mild symptoms before the final attack. Indeed, two children, aged 22 and 24 months respectively, died during their first severe episode of wheezing, illustrating the unpredictability of this condition in young children. All the remaining children had a history of severe asthma. A substantial proportion of children in groups III and IV had frequent nocturnal wheezing. Six cases in group IV were growth impaired—in one case, secondary to long term corticosteroid treatment.

MANAGEMENT BEFORE THE FATAL ATTACK

Treatment and control

Table 3 shows the long term treatment prescribed. Control was assessed according to the

Table 3 Routine drug treatment prescribed before onset of final illness (n=35)

Age (years)	Drug combination	No of children
<5	No regular treatment	2
	Antibiotic	1
	Oral bronchodilator	4
	Oral/nebulised bronchodilator plus nebulised sodium cromoglycate	3
	Oral bronchodilator plus adrenocorticotrophic hormone	1
≥5	No regular treatment	1
	Inhaled bronchodilator	5
	Inhaled bronchodilator plus sodium cromoglycate	3
	Inhaled bronchodilator plus beclomethasone	6 (3)*
	Inhaled bronchodilator plus sodium cromoglycate plus beclomethasone	4 (1)*
	Inhaled bronchodilator plus prednisolone/adrenocorticotrophic hormone	3 (1)*
	Inhaled bronchodilator plus beclomethasone plus prednisolone/adrenocorticotrophic hormone	2 (1)*

*Children receiving additional drugs—for example, theophylline or ketotifen.

following criteria: (i) frequency of attacks and exercise tolerance, according to parental history; (ii) missed schooling, often verified by school attendance records; (iii) peak flow rates where documented; and (iv) number of emergency consultations confirmed by hospital and practice notes. These factors were examined in relation to documented prescribed drug treatment. Allowance was made for the fact that nebulisers for the delivery of both bronchodilators and prophylactic drugs were not freely available until the early 1980s.

Fourteen of the 35 children had been adequately controlled until the onset of the fatal attack. Three children had suffered intractable asthma that responded poorly to all forms of maintenance treatment. The remaining 18 cases were poorly controlled, with the following deficiencies in treatment. (1) Seven children had not been prescribed adequate prophylaxis, and some had only occasional access to a bronchodilator. Antibiotics were frequently prescribed. (2) Four children who were normally well controlled deteriorated during the last two months of life and on medical consultation had been prescribed antibiotics only. (3) Four children, apparently compliant with prescribed treatment, might have benefited from long term systemic corticosteroid. (4) Three further cases had been instructed to stop long term corticosteroid within three months of death and had not been properly followed up.

Supervision

Nineteen children were attending hospital paediatric outpatient departments. Five cases were under the care of respiratory physicians. General practitioners alone were caring for 11 of the children, seven of whom had sufficiently severe asthma to warrant hospital referral. Frequency and severity of symptoms were often insufficiently documented, and the severity of asthma appeared to have been underestimated in the undertreated cases. Twenty eight of the 35 cases lived within easy reach of a general hospital, but only nine had been offered open access to the hospital ward in the event of a severe attack.

Home nebulisers

Eight children had been using home nebulisers and had died during the last six years of the study. Four were in their teens and the remainder were aged 7, 5, 3, and 2 years respectively. Nebulisers had been appropriately used in five children with difficult asthma. In the remaining three cases, supervision was poor and there had been frequent over-reliance on this form of treatment.

Family education

Parents were asked to recall the information they had received regarding their child's asthma during life. Nine sets of parents could recall having been given a proper explanation and specific instructions about the prescribed drugs. None had received written instructions other

than information on breathing exercises or house dust mite precautions. In the event of a severe attack, only 13 families had been instructed to obtain medical help promptly. None of the families interviewed recalled being made aware by professionals of the potential danger of a severe asthmatic attack in children, including parents of children who had previously experienced life threatening attacks.

THE FATAL EPISODE

Three children were found dead and details could not be obtained for one child who died while away from home. The length of the final attack in the remaining 31 cases was defined as the time between onset or notable increase in wheezing and cardiorespiratory arrest.

Deaths within three hours of onset (n=11)

These children died rapidly: six within 30 minutes of onset and five within three hours. There was avoidable delay in seeking medical help in one case. Two children suffered from permanent wheezing that was difficult to control even on maximal treatment. Four cases were inadequately controlled and their sudden severe attacks might have been prevented by better long term management. Five children were considered to be in reasonable control. Their rapidly fatal attacks occurred without prior warning. Six of the 11 had previously experienced a 'near fatal' attack. Nine of these rapid deaths occurred from 1980 to 1985 inclusive, but these numbers are too small to draw conclusions as to possible changes in the pattern of death with time.

Later deaths (n=20)

Death occurred between six and 72 hours after the onset of the attack (average length 24 hours). In these 20 cases there should have been time for treatment with adequate systemic corticosteroid to have been effective. Only two of these patients, however, had received appropriate amounts of corticosteroid before becoming moribund. Six of the 20 cases were either receiving long term systemic corticosteroid or had recently stopped such treatment. Corticosteroids had neither been increased nor recommenced during the final attack.

Thirteen cases died before reaching the hospital ward: either at home, in transit to hospital, or within 30 minutes of arrival in an accident and emergency department. Six of these children received no treatment over and above their usual oral or inhaled bronchodilator. The seven remaining children were either inadequately treated or were in extremis when the treatment was initiated. Delay or failure to seek medical help had occurred in nine of these 13 cases; in six of the 13, there had been an inappropriate medical response when help had been sought. One general practitioner had failed to attend, one child had been returned home from an accident and emergency department without proper assessment, and four cases were not referred to hospital.

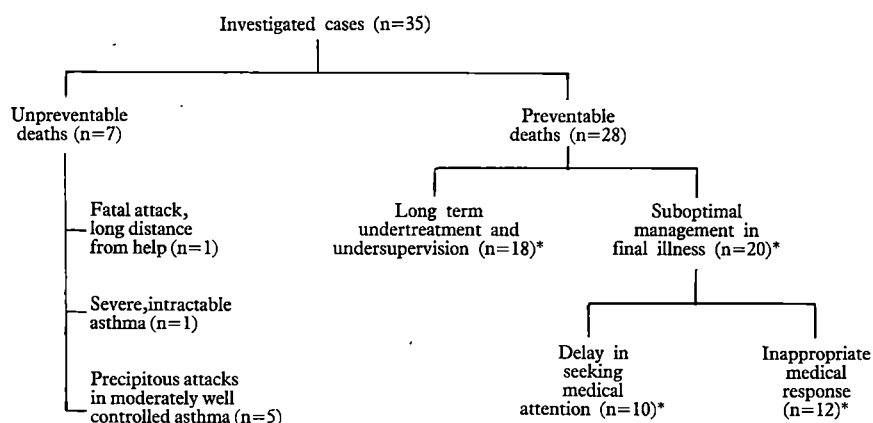


Figure 2 Summary of factors involved in deaths studied. *Factors overlapped in some cases.

There were seven inpatient deaths. Four children died between nine and 20 hours after hospital admission. One child suffered a respiratory arrest 2.5 hours after arrival and died some days later of irreversible brain damage. Two further children died after some weeks of inpatient care for stabilisation. Five hospital deaths occurred in children below 5 years of age, two of whom were diagnosed as 'wheezy bronchitis'.

With hindsight, six of the seven inpatient deaths might have been prevented had there been recognition of the severity of the condition, institution of more aggressive treatment, and possibly ventilation. In four cases systemic corticosteroid had been administered only when death appeared imminent, and bronchodilator treatment was often inadequate.

Despite the failed response to initial treatment and subsequent deterioration in all six cases, blood gas estimation had been performed in only one child.

CONCLUSIONS REGARDING OVERALL MANAGEMENT

If the overall care is examined critically then missed opportunities in management are identified in 28 of 35 cases. These factors are summarised in fig 2.

Discussion

Our survey suggests that with the knowledge of hindsight a high proportion of childhood asthma deaths are preventable, bearing out the findings of previous studies.^{3,4} In common with these studies, our survey was inevitably retrospective. A criticism of such a survey is the reliance in part on parental recall. However, parents' recollections of prescribed treatment were largely accurate when compared with case records. Most described convincingly the history of their child's symptoms and the effect on daily life and activities. Furthermore, they all recalled the circumstances of the final illness with particular clarity irrespective of how far back the event occurred. It is usual for such a traumatic event to be recalled with accuracy.

PREDICTABILITY

Six cases (17%) had experienced relatively mild

and infrequent symptoms before the onset of the final illness. Thus the widely held belief that only children with chronic severe asthma are at risk of dying is not true. Nevertheless, a recent controlled study of adult deaths highlighted the prognostic importance of a history of life threatening episodes or recent hospital admission.⁷ With hindsight, half the children in our study were obviously at risk of dying but this fact was insufficiently acknowledged at the time. Hospital discharge letters did not emphasise the life threatening nature of previous attacks, nor were parents properly instructed. Consultants should look critically at 'near miss' asthma deaths in order to take steps to reduce the risk of future fatal outcome.

LONG TERM TREATMENT AND SUPERVISION

Chronic undertreatment of asthmatic children is well documented and this,⁸ in association with poor supervision, was present in half our cases. They experienced a considerable amount of unnecessary morbidity. Clearly their fatal attacks might not have occurred had closer attention been paid to their long term management. Poor compliance may have influenced control in a few cases but this was impossible to investigate with accuracy. Over-reliance on inhaled bronchodilator was common. In three cases there was chronic over-reliance on home nebulisers. There has been a rapid increase in the use of these since the early 1980s and a number of near fatalities have been reported with their use.^{9,10} None of our deaths appear to have been related to a direct adverse effect of nebulised treatment, but nebuliser over-reliance in one case had led to fatal delay in seeking further medical help. While they are extremely useful in the home management of children with severe asthma, nebulisers should not be issued without proper education of parents and child and meticulous attention to long term control.

EMERGENCY MANAGEMENT

The single most important finding was that 20 children who died more than six hours after the onset of the fatal attack had not had access to optimal emergency treatment. The parents con-

sistently described to us very grave clinical signs but they had not been warned by professionals of the danger of such signs. Some families had become tolerant to severe symptoms while others, despite their anxiety, had been reluctant to call general practitioners at night or weekends. This was reflected by the excess number of weekend deaths. In cases where medical help had been sought, there appeared to have been similar difficulty on the part of professionals in recognising the severity of the condition and the urgent need for appropriate intervention.

PREVENTION OF SEVERE ATTACKS

Short courses of systemic corticosteroid are standard in the management of severe asthmatic attacks and this was so during the period of study. Work published recently has shown the efficacy of oral corticosteroid in speeding recovery and preventing dangerous deterioration in childhood asthmatic attacks.^{11 12} The use of self initiated courses of oral corticosteroid is accepted practice in the management of adult asthmatics but some paediatricians have tended to be reluctant to apply this to children. Such treatment does not generally cause significant long term hypothalamo-pituitary-adrenal axis suppression. In our analysis we estimated that a parent or patient initiated course of oral corticosteroid might have altered the outcome in at least 20 cases.

RECOMMENDATIONS

(1) It is imperative that all asthmatic children and their families receive proper education regarding control and self management. Clear written instructions should be provided and reinforced during hospital and practice contacts. Families should be taught how to recognise deteriorating control both clinically and by measurement of peak flow in older children.

(2) Families should have access to a simple method of delivery of bronchodilator in a high dosage to a breathless child, for example, the 'coffee cup' method, or spacer devices.¹³⁻¹⁵

(3) Parents of children receiving inhaled corticosteroid or who have previously suffered a

severe attack, should be instructed to initiate a course of oral prednisolone if the attack fails to respond to usual treatment.

(4) Those responsible for the child should know when and how to seek urgent medical help. They should be familiar with danger signs such as breathlessness sufficient to prevent talking, extreme pallor or cyanosis, poor chest movement or increasing lethargy and exhaustion, and should have free access to their local hospital.

(5) Hospitals should have a written management policy for the emergency treatment of children with asthma. This should include early use of systemic corticosteroid.

Implementation of these recommendations would, we believe, contribute to a significant reduction in this unnecessary mortality.

We are grateful to Miss M Trotter for secretarial help and to Drs RAL Brewis and EN Hey for helpful advice.

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Estimation of lung volume in infants by echo planar imaging and total body plethysmography

B Chapman, C O'Callaghan, R Coxon, P Glover, G Jaroszkiewicz, A Howseman, P Mansfield, P Small, A D Milner, R E Coupland

Abstract

Echo planar imaging (an extremely fast method of magnetic resonance imaging) was used to measure lung volume in a group of nine infants, all of whom had had respiratory problems. The mean echo planar imaging estimate of total lung volume was 44 ± 9 ml/kg. In each case the right lung was larger than the left (ratio 52.8:47.2%). The mean thoracic gas volume was 36 ± 8 ml/kg. The entire sequence of images of the thorax (about 400) takes five minutes to complete, infants require no sedation, and there are no side effects.

Echo planar imaging is a form of nuclear magnetic resonance imaging that gives short image acquisition times and so permits a sequence of images to be obtained rapidly. Each image is displayed in transection as it is acquired in real time.¹⁻³

We have used echo planar imaging to study the thoraxes of nine infants aged between 1 and 9 months, all of whom had had respiratory problems. The measurements were produced on our home built imaging machine operating at a field strength of 0.1 Tesla (T) which corresponds to an operating radio frequency of 4.0 MHz for protons.

We have compared the results of echo planar imaging for total and individual lung volumes with mean thoracic gas volume measurements. Measurement of thoracic gas volume in infancy by total body plethysmography after bronchiolitis has, however, recently been questioned by Godfrey *et al.*⁴ The work described here is an extension of an earlier pilot study.⁵

Patients and methods

Nine infants with recurrent attacks of wheezing were studied (table 1). Cases 8 and 9 had mild wheezes on auscultation; the other patients were clinically well when studied. Cases 2, 5, 7, and 8 were studied immediately before discharge from hospital after their wheezing had improved. Measurements of lung volume by plethysmography and by echo planar imaging were made on the same day in cases 4-9 and within two days of each other in cases 2 and 3. Case 9 was studied at 1 and 3 months of age. Case 1 did not have the thoracic gas volume measured.

Infants were sedated with chloral hydrate (120 mg/kg) to allow measurement of thoracic gas volume by total body plethysmography.⁶⁻⁹ The total body plethysmograph had a capacity

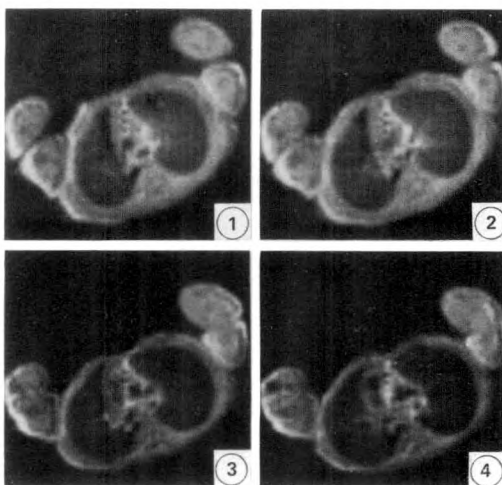
Table 1 Details of patients studied

Case No	Age (months)	History of bronchiolitis
1	8	Yes
2	4	Yes
3	9	Yes
4	8	No
5*	6	Yes
6	6	No
7	10	Yes
8	10	Yes
9 (at 1 month old)	2	No
9 (at 3 months old)	4	No

*Case No 5 was the only girl studied.

of 260 l and a servocontrolled heating system to maintain the face mask, shutter system, and rebreathing bag at 36°C. Thoracic gas volume was measured after inspiration, with subtraction of the tidal volume after calculation. Each child was nursed supine and a latex face mask was applied; this was smeared with petroleum jelly to help secure an airtight seal. The dead space of the mask was 55 ml for patients 1-8, but a 28 ml mask was used for patient 9. There was a bias flow of air to the face mask of 5 l/minute. Signals were relayed to the axes of a cathode ray oscilloscope, readings were taken by the same observer, and calculations made by standard techniques. From five to eight breaths were analysed in each case.

Infants required no sedation for echo planar imaging studies. The echo planar imaging technique is an extension of nuclear magnetic resonance imaging and the details of its develop-



Four contiguous echo planar transectional images through the mediastinum of an infant. The patient's left side is on the left.

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Table 2 Comparison of measured thoracic gas volume by total body plethysmography with total lung volume measurement by echo planar imaging. Also shown is airways resistance

Case No	Thoracic gas volume (ml/kg)	Airways resistance (cm H ₂ O/l/s)	Lung volume measured by echo planar imaging		
			Total volume (ml/kg)	Left lung (ml)	Right lung (ml)
1	Not measured	Not measured	29	50	54
2	29	60	50	200	161
3	37	27	45	110	113
4	37	21.7	43	120	195
5	34	33	36	136	145
6	34	19	38	159	185
7	60	60	69	154	155
8	27	45	41	110	138
9 (at 1 month old)	85	31.4	58	119	120
9 (at 3 months old)	70	55	55	156	205

ment and medical use may be found elsewhere.¹⁻³

The procedure requires no gating, because each image is a snapshot acquired within 32 to 64 ms. It is therefore comparatively free of motional artefact from either cardiac or respiratory movement. Each transectional image is 6 mm thick. A 64×64 pixel display was used resulting in a true resolution within each slice of 3 mm. Consecutive images are acquired during the cardiac cycle with the first image of each sequence triggered by the QRS complex of the electrocardiogram.

A Winchester quart of known transectional area was used as the standard. The area obtained from this image was measured by planimetry and compared with the known area. A conversion factor was determined and used to convert image screen measurements of lung area to actual size. The same standard was repeated before each study.

The accuracy of area measurement had two components: an inherent error (ϵ_i), which is related to the pixel signal:noise ratio (R) and calculated by $100/(R\sqrt{N})\%$, where N is the number of pixels scanned in the area of interest, and an observer error (ϵ_o), which arises from errors in delineating the area of interest and reproducibility. The inherent error is usually around 1%, whereas the observer error is about 10%.

The initial transectional image was obtained at the apex of the lung and at 6 mm steps towards the base until lung was no longer seen. Numbers of slices ranged from 10–16, depending on the patient. The area of the lung at each stage was measured by planimetry, converted to actual area, and multiplied by the stage thickness to give total and individual estimates of lung volume. Each transectional image measured was a compilation of 16 snapshots taken in rapid succession (figure), so the lung volumes calculated tend to reflect volume in the middle of a tidal breath. All readings were made by the same observer.

This study was approved by the Nottingham ethics committee. Written parental consent was obtained for the observations.

Results

None of the infants required sedation for echo planar imaging studies, each of which took less than five minutes to carry out.

The measurements of thoracic gas volume

and airways resistance, and measurements of individual and total lung volume using echo planar imaging, are shown in table 2.

The mean thoracic gas volume was 36 ± 8 ml/kg. The estimate of total lung volume by echo planar imaging was 44 ± 9 ml/kg.

Taking the group as a whole, 47.2% of the total lung volume was in the left lung and 52.8% was in the right lung according to the echo planar imaging. The coefficient of variation for intrasubject measurement of thoracic gas volume was 4.1%.

Discussion

Measurement of thoracic gas volume in infants by total body plethysmography requires sedation and can be a lengthy procedure. In addition, measurement of thoracic gas volume when airways are closed,⁵ and measurement in wheezy infants who have had bronchiolitis, has been questioned.⁴ The use of an imaging technique to calculate total, and—for the first time—individual, lung volumes in this age group is appealing. Magnetic resonance imaging has no known hazards and studies of the thoraxes of infants using echo planar imaging can be completed within five minutes with no need for sedation.

The plethysmographic measurement and the echo planar imaging estimates differ. Measurements of lung volume obtained by echo planar imaging include volume taken up by lung tissue, hence they should be greater than measurements of thoracic gas volume. In addition measurements of thoracic gas volume were made after inspiration, with subtraction of the tidal volume after calculation, but echo planar imaging measurements were made at what we consider to be mid tidal volume. Thus, in addition to lung tissue volume, they may be expected to be half a tidal volume greater than thoracic gas volume. Using echo planar imaging, only part of the dead space is measured, which we ignore in these results. Dead space in infancy has been measured by various groups, and estimates range from 1.1–2.77 ml/kg.¹⁰⁻¹³

In cases 2–8 the lung volumes on echo planar imaging were between 2 and 21 ml/kg greater than the measurements of thoracic gas volume. Only in case 9 was the thoracic gas volume larger than the echo planar imaging estimation of total lung volume. In this patient a different face mask with a dead space of 28 ml (as

opposed to 55 ml) was used. When the infant was sedated it was impossible to obtain a complete seal with our standard mask. It is interesting that previous studies have shown that this mask gives measurements of thoracic gas volume up to a third higher than the mask we usually use, with a dead space of 55 ml. Whether the difference is the result of using the small face mask, or of some other effect, remains to be determined.

The right lung was of greater volume than the left lung in all cases except case 2, in whom the left lung was 39 ml larger. Echo planar imaging showed collapse and consolidation in the right lung, which was responsible for the reduced right lung volume. Omitting this patient's results, the mean right lung volumes of the group were between 50% and 62% of the total lung volumes. This finding is similar to the results of weighing normal lungs at necropsy. Emery and Mithal found the right lung weighed between 52–57% of the total lung weight in babies between the ages of 1–12 months.¹⁴ Cases 8 and 9 had mild wheeze at the time of the study, and were clinically hyperinflated. Their lung volume estimates agree with the clinical assessment (table 2). The use of this method to study individual lung volumes will be of great interest in monitoring lung growth in infants with hypoplastic lungs and after repair of diaphragmatic hernias,¹⁵ as well as in measuring the effects of scoliosis on lung volume, and in many other conditions.

The images obtained from the more hyperinflated babies seemed less dense than those from the other infants. With improvements in image quality it will be possible to measure the density of the lungs from the echo planar

images. Studies are being conducted in older subjects to equate the density reading with actual tissue volume.

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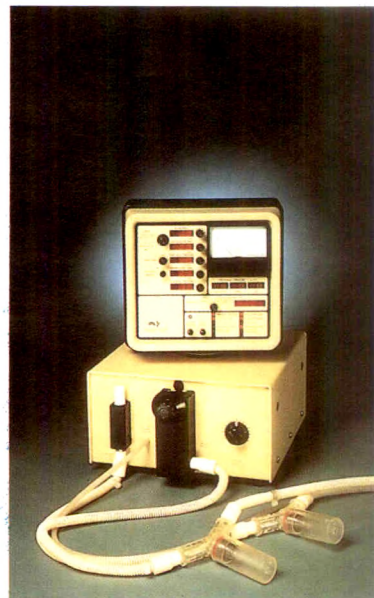


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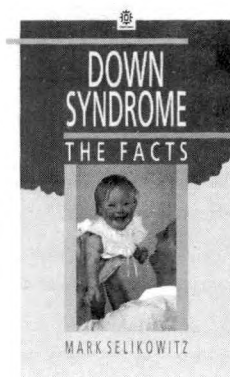
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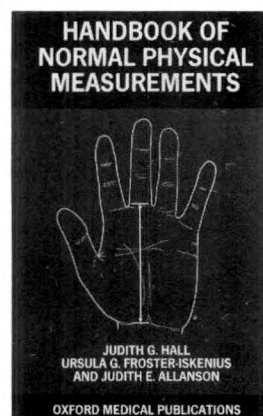
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Airway function in infants with vascular rings: preoperative and postoperative assessment

A H Thomson, C S Beardsmore, R Firmin, R Leanage, H Simpson

Abstract

Aortic arch anomalies in infancy often cause intrathoracic airway obstruction. Airway function was assessed as part of the diagnostic evaluation in six symptomatic infants both by plethysmography and using a chest compression technique to obtain partial flow-volume loops. Two infants had normal intrathoracic airway function and their symptoms were unrelated to aortic arch abnormalities. The remaining four had complete vascular rings (three double aortic arch, one pulmonary sling) and had increased expiratory airway resistance (R_{aw}) (mean R_{aw} =700% predicted) and greatly decreased maximum flow rates at functional residual capacity ($\dot{V}_{maxFRC}$; mean $\dot{V}_{maxFRC}$ =34% predicted) with gross shape abnormalities of the flow-volume loop. Postoperatively airway function was substantially improved (mean R_{aw} =175% predicted, $\dot{V}_{maxFRC}$ =79% predicted) but some abnormality of flow-volume loop shape remained, suggesting that tracheal dynamics were not completely normal in the early postoperative period.

Anomalies of the aortic arch complex account for less than 1% of congenital cardiac malformations but frequently cause airway obstruction presenting in infancy. Surgical division of a vascular ring, first reported in 1945,¹ is now considered safe and effective in providing symptomatic relief. Two recent reports on the long term follow up of airway function after surgery for vascular ring, however, have shown residual lung function abnormalities in 55-80% of cases despite symptomatic improvement.^{2,3} Objective assessment of airway function before and after operation, which demonstrates the immediate effectiveness of surgical intervention, has not been reported previously.

Patients and methods

Over an 18 month period all six infants presenting to a regional centre with symptoms of airway obstruction in association with aortic arch anomalies had full lung function assessment as part of their diagnostic evaluation. Four of these infants required surgical treatment and repeat measurements were made at a mean of eight weeks postoperatively (six to 10 weeks). All were clinically stable and breathing room air at the time of the studies. Table 1 gives clinical details of the infants. The investigative approach to these infants with stridor was to examine the airway radiologically using a

Cincinnati filter and perform a barium swallow to look for indentation of the oesophagus in all cases. Laryngoscopy and bronchoscopy were performed selectively. All infants had cardiac catheterisation.

ASSESSMENT OF LUNG FUNCTION

The infants were sedated with chloral hydrate (60-100 mg/kg) and measurements made of thoracic gas volume (TGV) and airway resistance (R_{aw}) in a modified Jaeger whole body plethysmograph.⁴ Predicted values for TGV and R_{aw} were calculated from the equations: $TGV(ml) = -239 + 6.77 \times \text{length}(cm)$ and $R_{aw} = 1/Gaw$ (airway conductance); $Gaw = -0.47 + 0.016 \times \text{length}(cm)$ respectively (J Stocks, C Dezateaux, personal communication). Inspiratory resistance was calculated at 50% initial inspiratory flow and expiratory resistance was calculated at 50% end expiratory flow and expressed as a percentage of the predicted inspiratory values (predicted expiratory values unavailable). Partial expiratory flow-volume curves were obtained using a chest compression technique.⁵ Briefly, the infant was placed in a double thickness polythene jacket extending from shoulders to thighs and breathed through a facemask attached to a heated screen pneumotachograph. Tidal flow-volume loops were recorded and at the end of a normal inspiration the jacket was rapidly inflated causing chest compression and rapid expiratory flow. Forced partial expiratory flow-volume curves were thus obtained. The maximum flow rate at functional residual capacity ($\dot{V}_{maxFRC}$) and the ratio of forced maximum expiratory flow to tidal flow at midtidal volume ($\dot{V}_{mid}$ forced/tidal) were calculated. The single best value from the technically acceptable data is given for $\dot{V}_{maxFRC}$: predicted values were taken from Shulman *et al.*⁶

Results

GENERAL INVESTIGATION

The ring formed by a double aortic arch resulted in classical symptoms, signs, and appearances on radiography in cases 1, 2, and 3 (tables 1 and 2). The symptoms from a pulmonary sling in case 4 were more variable and the infant presented later in respiratory distress and with two episodes of 'collapse' before referral. A soft tissue shadow between the trachea and oesophagus was missed on the first barium swallow but found on a subsequent test after intrathoracic narrowing of the trachea had been shown on a Cincinnati airway view. The finding

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Table 1 Clinical details

Case No	Symptoms				Signs			
	Age at presentation (weeks)	Noisy breathing	Feeding difficulties	Apnoea	Stridor		Indrawing	Wheeze/rhonchi
					Inspiratory	Expiratory		
1	5	+	+	—	+	+	+	+
2	2	+	—	—	+	+	+	—
3	30	+	—	—	+	+	+	—
4	20	+	—	+	+	+	+	+
5	14	+	+	—	+	—	+	—
6	7	+	—	+	+	—	—	—

Present (+), absent (—).

Table 2 Results of investigations

Case No	Bronchoscopy	Barium swallow	Cincinnati views	Anatomical diagnosis
1	—	Posterior and left lateral compression of oesophagus	Trachea deviated to right	Complete double aortic arch of equal dimensions
2	Trachea narrow above carina	Posterior compression of oesophagus	Anteroposterior compression of trachea	Incomplete double aortic arch with ligament on left
3	—	Posterior and left lateral compression of oesophagus	Narrowing trachea above carina	Complete double aortic arch
4	—	(1) Normal (2) Soft tissue shadow between lower oesophagus and trachea	Narrowing intrathoracic trachea	Anomalous left pulmonary artery-pulmonary sling
5	Laryngomalacia, posterior indentation of trachea	Posterior compression of oesophagus	Normal	Left arch with anomalous right subclavian
6	—	Posterior compression of oesophagus	Normal	Left arch with anomalous right subclavian

of expiratory stridor on examination distinguished these four infants with aortic arch anomalies resulting in intrathoracic airways compression.

Case 5 had laryngomalacia but also indentation of the oesophagus on a barium swallow and a probable posterior indentation of the trachea at bronchoscopy, and in case 6 the severity of the symptoms and oesophageal indentation led to further investigation. Both infants were found to have left aortic arch with anomalous right subclavian vessels.

LUNG FUNCTION ASSESSMENT

Severe air flow limitation due to upper respiratory obstruction was demonstrated in five of the infants (table 3). Intrathoracic obstruction was the main problem in cases 1–3. The degree of airway obstruction was such that the thoracic gas volume could not be measured accurately in

case 1, while in all three infants Raw was appreciably raised during expiration (fig 1) even during tidal breathing. All demonstrated a profound decrease in forced expiratory flow rates as shown in fig 2a. Surgery resulted in dramatic improvement in airway function during both tidal and forced expiration (table 2, fig 2b) but all had some residual abnormality of flow-volume shape.

In case 4 no abnormalities were detectable during tidal breathing but a substantial decrease in VmaxFRC and extreme variability in maximum expiratory flow during each breath suggested a dynamic component to the airway narrowing, which was not observed in the other infants studied. There was a great improvement postoperatively, particularly in the forced expiratory flow rates, although the flow patterns were still variable.

Case 5 showed extrathoracic airway obstruction on lung function testing, with greatly

Table 3 Lung function results

Case No	Length (cm)	Thoracic gas volume (% predicted)	Raw (x% predicted)*		VmaxFRC (% predicted)	Midtidal expiratory: inspiratory ratio	Vmid forced/tidal ratio	Functional diagnosis	Time after operation (weeks)	Symptomatic improvement
			Inspiratory	Expiratory						
1 Preoperative	56.4	—	5†	40†	27	4 0.27(0.06)	1.00 (0.01)	Intrathoracic	9	Yes
Postoperative	61.8	88	2	2	76	4 0.63(0.14)	3.74 (0.51)	airways obstruction		
2 Preoperative	55	155	6	15	19	4 0.36(0.05)	1.00 (0.01)	Intrathoracic	7	Yes
Postoperative	62	92	0.5	1	90	5 0.57(0.04)	3.46 (0.41)	airways obstruction		
3 Preoperative	70.8	86	6	10	38	4 0.49(0.05)	1.89 (0.12)	Intrathoracic	6	Yes
Postoperative	71.8	81	1.5	2	53	4 0.55(0.07)	4.98 (0.42)	airways obstruction		
4 Preoperative	66.9	73	3	1	51	5 0.72(0.05)	1.91 (0.12)	Intrathoracic	10	Yes
Postoperative	69.5	89	2	2	97	4 0.59(0.06)	3.57 (0.38)	airways obstruction		
5 Test 1	58.5	104	21	3	96	6 0.61(0.06)	5.34 (0.68)	Extrathoracic	—	—
								airways obstruction		
6 Test 1	57.4	88	0.5	0.5	140	4 0.81(0.01)	4.10 (0.61)	Intermittent extrathoracic airways obstruction		

*Expressed as multiple of % predicted—that is, 5=500%.

†Approximate Raw (thoracic gas volume variable; mean value used for Raw calculation).

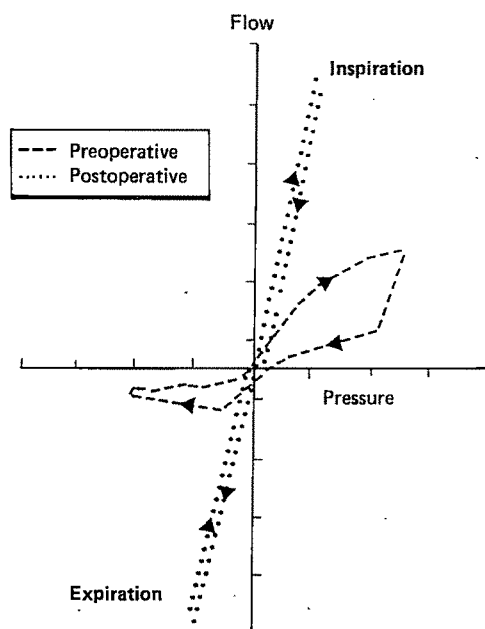


Figure 1 Pressure-flow curves from case 2 illustrating low flow rates despite high intrathoracic pressure preoperatively and a normal pressure flow curve postoperatively. Flow marker=40 ml/s, pressure marker=4 cmH₂O.

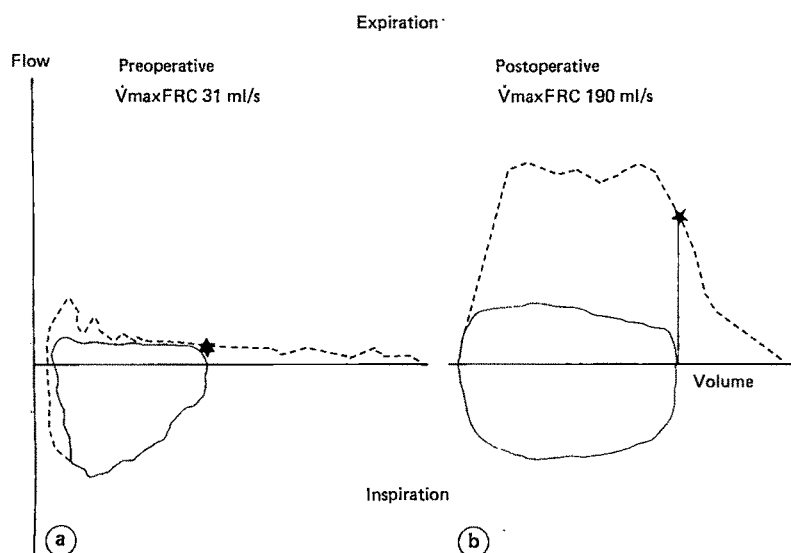


Figure 2 Flow-volume loops preoperatively and postoperatively in case 2.

increased inspiratory airways resistance, a normal thoracic gas volume, and normal $\dot{V}_{maxFRC}$. Case 6 had normal airway function. These two infants had an incomplete vascular ring and the demonstration of normal intrathoracic airways function provided reassurance that the aortic arch anomaly was not related to the symptomatology.

Discussion

Most children with a vascular ring present with respiratory difficulty. Those with severe airway obstruction are more likely to have an early presentation. Nevertheless, vascular rings form only a small proportion of the infants with noisy breathing from birth, most of whom have laryn-

gomalacia. A clinical clue in differentiation is expiratory as well as inspiratory stridor.

The cases presented illustrate that in the diagnosis of vascular ring there is no single diagnostic investigation. It was apparent at presentation that all the infants had upper airway obstruction. Clinical appraisal and investigation divided these into intrathoracic and extrathoracic obstruction. Respiratory function tests confirmed this distinction and documented the degree of airway dysfunction.

Airway function was assessed during both tidal breathing and forced expiration. Tidal flow-volume loops are technically easy to record in infancy and it has been suggested that they should be used in the evaluation of upper airway obstruction.⁷ This involves both pattern recognition and their objective numerical expiratory to inspiratory ratio. It is predictable that only infants with severe degrees of airway obstruction will demonstrate airflow abnormalities during tidal breathing and this was confirmed in our infants. Airways resistance, again measured during tidal breathing, is a much more sensitive test but infant whole body plethysmography is technically complex and time consuming. The patterns obtained from the airways resistance plots are more important than numerical data and clearly distinguish intrathoracic and extrathoracic obstruction, and the direction of the looping can describe the pathophysiology.⁸

A standardised technique for obtaining partial forced flow-volume loops in infancy has been developed, and the most commonly reported value is flow rate at functional residual capacity.^{5,9} Patterns of looping are less well described but a recent paper examined the importance of the shape of the curve when using a standardised compression pressure.¹⁰ A standardise compression pressure was not used in our infants but pressure adjusted to obtain the maximum flow rate for each infant. When airway obstruction is severe, flow limitation occurs even during tidal breathing (fig 2, case 2). A new parameter, introduced by Le Souef *et al.*,¹⁰ of the ratio of forced maximum expiratory flow to tidal flow at midtidal volume ($\dot{V}_{mid}$ forced/tidal) was also calculated in our patients and proved a good index of postoperative improvement. This parameter has the advantage of being a non-dimensional index of airflow obstruction unlike $\dot{V}_{maxFRC}$, which must be considered either as a percentage predicted based on infant length or size corrected by dividing by the absolute lung volume at functional residual capacity. Both forced expiratory flow rates at functional residual capacity and $\dot{V}_{mid}$ forced/tidal give a clear indication of airways reserve. It is important to remember, however, that from numerical details alone, major intrathoracic airways obstruction cannot be distinguished from peripheral airway obstruction and lung function must be interpreted in the context of clinical data.

Long term follow up studies of patients with vascular ring have shown residual lung function abnormalities in over 50%,³ even in those with complete resolution of symptoms.⁵ There was no association found between age at operation and outcome. The most severely compromised

trachea is likely to present early but less severe compression may be present for years before it is detected. The relative importance of these factors on tracheal growth is unknown. The long term function abnormalities on testing have been attributed to either residual tracheomalacia or local tracheostenosis despite the relief of compression. Early postoperative airway assessment and subsequent follow up may provide evidence on the relative importance of these factors.

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Volume 149 No. 2 1989

The pioneers of pediatric medicine 75

Review

Somatomedin-binding proteins: what role do they play in the growth process?
S. Cianfarani, J. M. P. Holly 76

Endocrinology

Long term feasibility of multiple daily injections with insulin pens in children and adolescents with diabetes
N. Tubiana-Rufi, C. Levy-Marchal, E. Mugnier, P. Czernichow 80

Autoimmune involvement in Cushing syndrome due to primary adrenocortical nodular dysplasia
H. Carstensen, S. Krabbe, N. M. Wulffraat, M. Damkjaer Nielsen, E. Ralfkiaer, H. A. Drexhage 84

Transient gall bladder dilatation associated with hypokalaemia in a patient with Bartter syndrome
A. Goren, R. Drachman, I. Hadas-Halperin, A. Drukker 88

Congenital hypothyroidism and partial thyroid hormone unresponsiveness of the pituitary in a patient with congenital thyroxine binding albumin elevation
S. L. S. Drop, E. P. Krenning, R. Docter, S. M. P. F. de Muinck Keizer-Schrama, T. J. Visser, G. Hennemann 90

Imaging techniques

Ultrasonic evaluation of kidney length in term and preterm infants
A. Chiara, G. Chirico, M. Barbarini, E. De Vecchi, G. Rondini 94

Immunology/Allergology

The DiGeorge sequence. II. Immunologic findings in partial and complete forms of the disorder
W. Müller, H. H. Peter, H. C. Kalfelz, A. Franz, C. H. L. Rieger 96

HLA-haploidentical bone marrow transplantation in three infants with adenosine deaminase deficiency: stable immunological reconstitution and reversal of skeletal abnormalities
R. Bluetters-Sawatzki, W. Friedrich, W. Ebell, U. Vetter, H. Stoess, S. F. Goldmann, E. Kleihauer 104

Infectious diseases

Osteomyelitis-like bone lesions in acne fulminans
S.-L. Pauli, T. Valkeakari, L. Räsänen, M.-L. Tuomi, T. Reunala 110

Prolonged and secondary fever in childhood bacterial meningitis
A. S. Daoud, M. Zaki, Q. A. Al-Saleh 114

Medical genetics

Familial combination of brachydactyly, type E and atrial septal defect, type II
A. Czeizel, P. Göblyös 117

Metabolic diseases

Direct detection of a major mutation responsible for phenylketonuria in the population of the Federal Republic of Germany
U. Lichter-Konecki, M. Schlotter, F. K. Trefz, D. S. Konecki 120

Neonatology

Renal vein thrombosis and response to therapy in a newborn due to protein C deficiency
P. C. J. Rogers, M. P. Silva, J. E. J. Carter, L. D. Wadsworth 124

Nutrition

Fat absorption in premature infants: the effect of lard and antibiotics
H. J. Verkade, W. A. van Asselt, R. J. Vonk, C. M. A. Bijleveld, J. Fernandes, H. de Jong, V. Fidler, A. Okken 126

The offspring of mothers with anorexia nervosa: a high-risk group for undernutrition and stunting?
G. van Wezel-Meijler, J. M. Wit 130

Pharmacology

Dosage of nifedipine in hypertensive crises of infants and children
J. Lopez-Herce, P. Dorao, P. de la Oliva, M. A. Delgado, M. C. Martinez, F. Ruza 136

Pharmacokinetics of intra-arterial indomethacin treatment for patent ductus arteriosus
M. Weninger, A. Pollak, U. Salzer-Muhar, K. A. Vergesslich, H. R. Salzer 138

Letters to the editors

Intestinal milk-bolus obstruction in premature infants
B. Koletzko 141

Reply
J. K. H. Wales 142

Ascites related to cytomegalovirus infection
S. Özsoylu, N. Kocak, A. Yüce 142

Reply
I. Levy, Y. Levy 143

Hypogammaglobulinaemia in DiGeorge sequence
A. Etzioni, S. Pollack 143

Reply
M. Mayumi, H. Mikawa 144

Diameter of coronary arteries in infancy
S. Musumeci, G. Giordano, A. D'Agata 144

Reply
R. Oberhoffer 144

Hypercalciuria and nephrolithiasis in Wilson disease
N. Itami, Y. Akutsu, H. Tochimarui, Y. Takekoshi 145

Reply
E. Azizi 145

Autoimmune thyroiditis presenting as painful thyroiditis
A. K. Leung, K. Hegde 146

Simple method of umbilical artery catheterization
R. Lauterbach 146

Seasonal variations of glycosylated haemoglobin in diabetic children
A. Verrotti, F. Chiarelli, S. Tumini, G. Morgese 146

Reply
F. R. J. Hinde 147

Abstracts

The Summer Meeting of the Scottish Paediatric Society, Irvine, May 26, 1989 148

Indexed in *Current Contents*



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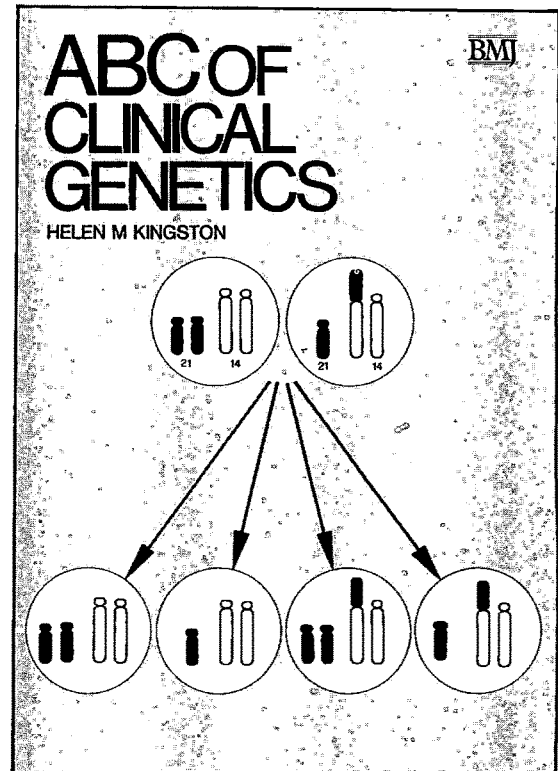
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Genetics is a subject fundamental to medicine, but rapid advances in recent years may make the subject complex and confusing to clinicians and paramedical staff outside the specialty. Nevertheless, the demand for genetic investigation and counselling is increasing, and these services need to be offered by clinicians other than clinical geneticists. In the *ABC of Clinical Genetics* Helen Kingston, consultant clinical geneticist at St. Mary's Hospital, Manchester, reviews basic concepts of inheritance in mendelian, chromosomal, and multifactorial disorders; outlines the investigation and management of genetic conditions; and illustrates the application of recombinant DNA technology to clinical practice. Implications of genetic diseases for relatives are also considered, together with the ethical and human dilemmas that face doctors and patients and their families.



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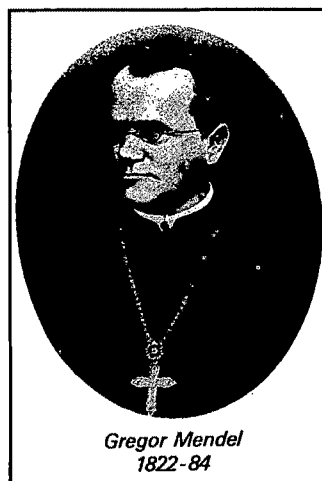
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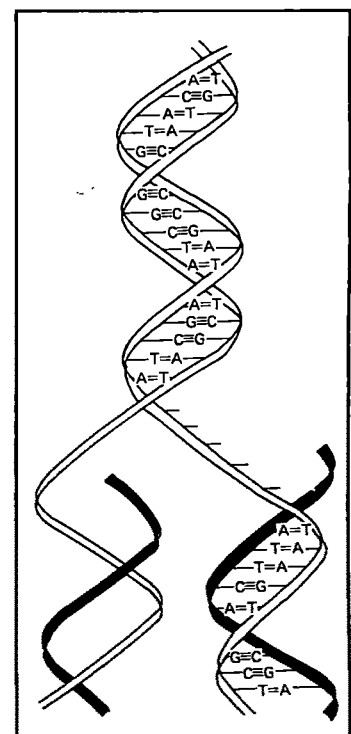
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Bacterial reservoirs in cystic fibrosis

C J Taylor, J McGaw, R Howden, B I Duerden, P S Baxter

Abstract

To establish whether colonisation of the upper respiratory tract or bacterial contamination of inhaler devices or solutions predisposes to colonisation of the lower respiratory tract in patients with cystic fibrosis, bacterial isolates from groups of children who were positive (n=13) or negative (n=18) for *Pseudomonas aeruginosa* were studied. Cultures of swabs from inhaler devices, toothbrushes, and upper airways were compared with cough swabs or sputum cultures. No pathogens were obtained from inhaler equipment administering unit dose medications. Upper airway carriage of *Staphylococcus aureus* and *Haemophilus influenzae* was identified in both groups but correlated poorly with sputum isolates. *P. aeruginosa* was found only in the upper respiratory tract of children with established colonisation of the lower airways. No *P. aeruginosa* isolates were obtained from the upper airways of the group with negative sputum, including one patient who became colonised by *P. aeruginosa* during the study.

Our results did not support the suggestion that colonisation of the upper respiratory tract by *P. aeruginosa* predisposes to colonisation of the lower airways. Failure to isolate pathogenic organisms consistently from the upper airways in patients with positive sputum argues against a local epithelial factor predisposing to bacterial colonisation.

The upper respiratory tract has a normal flora that varies with time and includes some of the pathogens associated with cystic fibrosis, although there are species differences—for example, capsulate or non-capsulate *Haemophilus influenzae*.¹ *Pseudomonas* spp may also be part of the normal upper airways' flora in both normal subjects and patients with cystic fibrosis.² It has been suggested that, in cystic fibrosis, colonisation of the upper respiratory tract may precede spread to the lower airways.³ Once established in the lungs the organism is extremely difficult to eradicate, therefore treating the infection at an early stage, possibly when it is confined to the upper airways, is an attractive proposition.

Many children with cystic fibrosis also use inhaled treatment. Shortly after the introduction of nebulisers, an increase of necrotising Gram negative pneumonias was noted in normal patients.⁴ Gram negative organisms, in particular *Pseudomonas* spp were also found in nebuliser reservoirs and solutions.^{5,6} Therefore we con-

sidered it appropriate to investigate the upper respiratory tract flora in children with cystic fibrosis to determine whether colonisation of the upper airways with *Pseudomonas aeruginosa* could be identified before sputum conversion and to examine inhaler equipment for contamination by pathogenic organisms.

Patients and methods

Chronic colonisation by *P. aeruginosa* was identified in 29 (40%) of the 73 children attending the cystic fibrosis clinic at Sheffield Children's Hospital. Thirteen consecutive clinic attenders in this group were studied (patients with positive sputum). Of the remainder, 18, from whom *P. aeruginosa* had never been grown (patients with negative sputum) also agreed to participate in the study. At a monthly clinic visit dry swabs were collected from the anterior and posterior nasal space and the back of tongue. After physiotherapy a sputum sample or cough swab, or both, was taken as appropriate. Parents were requested by letter to bring nebulisers, Spinhalers (Fisons), Rotahalers (Allen and Hanburys), jet inhalers, and toothbrushes with them to the clinic. Swabs were taken from these devices for bacteriological culture. Media used were blood agar incubated in air plus 5% carbon dioxide, heated blood agar with a bacitracin disk (8 µg) incubated anaerobically, CDMI agar,⁷ and cystine-lactose electrolyte deficient agar cultured aerobically. After incubation for 24 hours, plates were examined and colonies of potential pathogens were tested by standard procedures for reaction in Gram stain and production of coagulase, deoxyribonuclease, and oxidase for the recognition of *Staphylococcus aureus* and *P. aeruginosa*. *H. influenzae* was identified by a requirement for X and V factors in a disk test. Biochemical identification of 'coliform bacilli' included tests for indole, the Voges-Proskauer reaction, citrate utilisation, urease, and the o-nitrophenol-galactopyranoside test; these were confirmed, when necessary, by the API 20E system (Api-Bio Merieux).

Results

Results were recorded as shown in table 1. The recovery of the major bacterial pathogens for both groups is summarised in table 2. As expected the children in the group negative for *P. aeruginosa* were younger (mean age 8.3 years, range 3.3-14.6) with minimal or non-productive cough compared with the patients who were positive (mean age 11.9 years, range 6.5-17.5). Sputum cultures were often difficult to obtain

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Table 1 Example of bacterial harvest from a single site (toothbrush), showing the number of patients from results of both direct culture and broth incubation for groups of patients positive and negative for *P aeruginosa*

	Direct culture		Broth incubation	
	Positive patients	Negative patients	Positive patients	Negative patients
<i>Staphylococcus epidermidis</i>	3	2	2	3
<i>Streptococcus viridans</i>	3	1		4
Non-haemolytic			3	
Anaerobes: spore bearer			1	1
Diphtheroids	1		1	
<i>Neisseria</i> spp				1
<i>Escherichia coli</i>	1	3	1	3
Coliform bacilli	2		3	4
<i>Klebsiella</i> spp	2		1	
<i>Pseudomonas fluorescens</i>	3	1		
<i>Aeromonas hydrophilia</i>	1			
<i>H parainfluenzae</i>	1	1		
Non-lactose fermenting bacilli			1	2
No growth	4		1	

Other organisms sought but not isolated included: *S aureus*, α and β haemolytic streptococci, *Streptococcus pneumoniae*, *Streptococcus faecalis*, *H influenzae*, *Haemophilus parahaemolyticus*, bacteroides, and fungi.

Table 2 Number of patients with major bacterial isolates in groups positive and negative for *P aeruginosa*

	Toothbrush*	Rotahaler†	Nasal spray‡	PEP mask§	Nebuliser	Anterior nasal¶	Posterior nasal**	Tongue††	Cough swab‡‡	Sputum
Patients negative for <i>P aeruginosa</i> (n=18)										
<i>S aureus</i>						3	3		2	1
<i>H parainfluenzae</i>	1						1	3	3	1
<i>H influenzae</i>		Nil from 6	Nil from 2		Nil from 2	2	3		1	3
<i>P aeruginosa</i>										1
<i>Pseudomonas cepacia</i>										
<i>Pseudomonas</i> spp										
Patients positive for <i>P aeruginosa</i> (n=13)										
<i>S aureus</i>						1	1	2	4	5
<i>H parainfluenzae</i>	1									
<i>H influenzae</i>		Nil from 6	Nil from 2		Nil from 8			5	1	2
<i>P aeruginosa</i>									10	12
<i>Pseudomonas cepacia</i>										1
<i>Pseudomonas</i> spp										

Samples taken from: *between bristles with moist swabs; †inside mouthpiece with moist swab; ‡outside and inside nosepiece with moist swabs; §internal green and yellow surfaces of valve with moist swab, internal wall of resistor arm with moist swab; ||lower chamber with moist swab; ¶dry swab before physiotherapy; **3 cm posterior and lateral with dry swab; ††back of tongue with dry swab before physiotherapy; ‡‡deep throat with dry swab after physiotherapy; ||||patient after physiotherapy.

in the former group; only cough swabs were possible in 10.

There was a high correlation between cultures from cough swabs and isolates from the dorsum of tongue in both groups and also with sputum cultures in the group positive for *P aeruginosa*. *S aureus* was isolated from anterior and posterior nasal swabs from three of the negative group but not from the sputum. One was a regular user of a nasal spray from which *S aureus* was also cultured. A further three patients had positive cultures from either sputum or cough swabs but not nasal carriage. One child was sputum positive for *H influenzae* with nasal carriage, two others had positive sputum cultures but no nasal isolates. *H influenzae* was isolated from the posterior nasal space of two further children but they gave negative sputum cultures. *Haemophilus parainfluenzae* was grown from sputum or cough swabs from five patients, only one of whom had nasal carriage. A single patient carried the organism in the posterior nares and dorsum of tongue but had clear sputum cultures. *P aeruginosa* was not isolated from the upper airway of any child in the group with negative sputum, including the one patient who became sputum positive during the study.

In the group positive for *P aeruginosa* there was good correlation between the results of cough swabs and sputum isolates. Except for two children who could not produce a sputum

sample, *P aeruginosa* was isolated from sputum cultures of all who had positive cough swabs. *P aeruginosa* was also found in nasal swabs from one patient.

Discussion

Pulmonary infection with *P aeruginosa* is a major cause of morbidity and subsequent mortality in patients with cystic fibrosis.⁸ Once the organism is established in the lungs attempts to eradicate it are rarely successful, although transient bacterial clearance and improvement in respiratory function can be achieved with either inhaled⁹ or intravenous antibiotics.¹⁰ However, most patients will revert to being sputum positive within three months of treatment.⁹

If colonisation of the upper airways precedes pulmonary invasion, it may be argued that appropriate antibiotic treatment at this stage may prevent or delay pulmonary disease. Parallels with *P aeruginosa* colonisation of endotracheal tubes in intensive care settings have been drawn, with the success of selective bacterial decontamination in these patients being proposed as a precedent for similar treatment in cystic fibrosis.¹¹ Support for this theory is drawn from studies by Lindemann *et al*¹² and Komiyama *et al*³ who were able to obtain positive cultures from the oral cavity in cystic

fibrosis sufferers. Komiyama *et al* also obtained growths from dental plaque but *P. aeruginosa* was not isolated from this site by Lindemann *et al*. As the mean age in the former study was 19 years and in the latter was 13.5 years, it is likely that many if not all of the cystic fibrosis subjects studied had chronic *P. aeruginosa* lung colonisation. The importance of positive cultures from the oral cavity in such patients is therefore uncertain. Neither study purports to have examined children before they became sputum positive. Iacocca *et al* have already shown that isolation of an organism from deep throat or nasopharyngeal swabs often reflects the presence of the organism below the larynx¹³; our findings show that the organism occurs only in the upper airways of patients with established lung colonisation. We were unable to demonstrate *P. aeruginosa* in the upper respiratory tract of any child in the absence of pulmonary involvement, even in the single child who became sputum positive during the study. The results of a single trial of selective decontamination of the nasopharynx have also proved unsuccessful (AM Dalzell, DP Heaf, HKF van Saene. Abstract presented at Cystic Fibrosis Research Workers Conference, Manchester 1988).¹⁴

The possibility that bacterial contamination of inhalation equipment may occur and act as an infectious reservoir was also explored. Aerosol solutions are frequently used in cystic fibrosis to administer bronchodilators and mucolytics before physiotherapy. Nebulised broad spectrum antibiotics are widely employed to reduce both the frequency of relapse in established *P. aeruginosa* infection and to prevent the progression from colonisation to infection.¹⁴ Microbial contamination of nebuliser treatment equipment has, however, been observed with both home and hospital usage.^{5 6 15 16} Studies suggest that contamination is most likely with multiple dose solutions rather than unit dose medications. However, both bronchodilator and antibiotic solutions can be affected; the presence of bacteriostatic agents in the drug solutions appears protective. Studies of equipment from patients with asthma or chronic obstructive airways disease have usually yielded environmental organisms, however *Pseudomonas* spp were found in 8–54%, the latter higher figure occurring in a burns unit.¹⁷ The lack of positive cultures from inhalation equipment in this study reflects the use of single dose medications. Multiple dose aerosols were given only as nasal sprays. Three of the study population used these devices, one of which showed contamination with *S. aureus*; this child also had nasal carriage. Although little can be drawn from such a small sample, the limited ability to clean adequately such multidose systems should be considered. We could find no evidence to

implicate aqueous sprays from toothbrushes as a source of infection.

Overall we have shown a poor correlation between upper airways carriage of bacteria and sputum positivity. There was a good correlation between sputum positivity and isolation of pathogens from cough swabs, however, confirming the appropriateness of this technique in young children unable to produce sputum voluntarily. We have found no evidence to suggest that colonisation of the upper airways, particularly with *P. aeruginosa*, precedes lower respiratory tract invasion. Therefore, prophylaxis to prevent this colonisation would seem inappropriate until a longitudinal study establishes a link between the two events. With <5% of patients with cystic fibrosis becoming positive for *P. aeruginosa* each year, a multi-centre study would appear necessary. As the floor of the nose shows the same abnormality of ion transport as the lungs in cystic fibrosis,¹⁸ the lack of colonisation suggests that local epithelial factors do not predispose to chronic infection.

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Ontogeny of pancreatic exocrine function

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Abstract

Exocrine pancreatic proteolytic activity, determined by serial measurement of faecal chymotrypsin concentration, was investigated in 21 preterm infants (23-32 weeks' gestation) during the first 28 days of life. The overall chymotrypsin concentration range was similar to that already described in term infants showing that pancreatic chymotrypsin secretion is equally well developed at birth in the preterm infant. A chymotrypsin concentration peak, seen in term infants at 4 days, did not occur in this study until day 8, suggesting a slower initiation of pancreatic exocrine function in the preterm infant. Median faecal chymotrypsin concentrations, calculated for each baby using data from stools passed between day 2 and day 12 of life, were significantly lower in infants who were small for gestational age when compared with those who were an appropriate size for gestational age. The lower chymotrypsin concentration in infants who were small for gestational age suggests a deleterious effect of intrauterine growth retardation on pancreatic exocrine function which may be a factor in limiting postnatal catch up growth.

The effect of postnatal feeding and other environmental factors on the ontogeny of the gastrointestinal tract is clearly important for survival of the preterm neonate. This is even more important in preterm infants with intrauterine growth retardation who may be less able to absorb nutrients than appropriately grown infants,¹ and who may have suboptimal growth throughout life. Such children are three times more likely than non-growth retarded babies to die during the first year of life.² It has been suggested that by compromising nutrient digestion and absorption, intrauterine growth retardation may play an important part in subsequent poor postnatal growth.³ While few data are available from studies in humans, animal investigations have shown a clear association between intrauterine growth retardation and depression of exocrine pancreatic function.⁴ Severely affected infants may therefore suffer an additional disadvantage through relative pancreatic exocrine insufficiency.

Intraduodenal tests are the most accurate method for determining exocrine pancreatic function,⁵ but they are clearly inappropriate for repeated investigation of preterm neonates being invasive, expensive, and technically complex. In contrast, faecal chymotrypsin measurement is non-invasive, cheap and simple,⁶ and it

is therefore ideal for repeated use in longitudinal studies. A recent study from this department has shown that there is a strong positive correlation between apparent pancreatic chymotrypsin and trypsin secretion rates after intravenous pancreozymin-secretin and faecal chymotrypsin concentrations.⁷ We have therefore used serial measurements of chymotrypsin concentrations in stool to investigate the development of pancreatic secretory capacity over the first few weeks of life in preterm neonates who were either appropriate (AGA) or small for gestational age (SGA).

Subjects and methods

Twenty one preterm infants of 32 weeks' gestation or less (median gestational age 30 weeks, range 23-32), consecutively admitted to a regional neonatal intensive care unit, were included in the study from birth. The median birth weight was 1210 g (range 590-2100). Fourteen infants were normally grown (AGA), while seven showed evidence of intrauterine malnutrition with weight less than the 10th centile for gestational age (SGA). Gestational ages in the infants in the AGA group (26-32 weeks) and SGA group (23-32 weeks) were similar ($p > 0.1$). The assessment of gestational age was based on clinical examination performed on the first day of life,⁸ together with reference to routine early antenatal ultrasonic measurements.⁹

All infants received milk volumes related to their body weight: 60 ml/kg for the first two days of life, increasing by 30 ml/kg every two days to a total of 150 ml/kg. Five received only expressed breast milk; 16 were given breast milk followed by Premium (Cow and Gate) or Pregestimil (Mead Johnson). Two babies were given parenteral nutrition during part of the study period. Two developed necrotising enterocolitis during the four week study period. The results from infants with necrotising enterocolitis are included in this report but excluded from the SGA-AGA comparison.

STOOL COLLECTION AND ANALYTICAL METHODS

Stool specimens were collected daily during the first three weeks of life and then twice during the final week. Occasional days were omitted in most babies but all babies were studied for a minimum of 10 days. Seven patients were transferred back to referring hospitals before completion of four weeks. Specimens were collected in polystyrene Fecon stool containers, and stored at -20°C until analysed. Chymo-

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tryptic activity was measured using the Haverback kinetic potentiometric method.⁶ Details of the procedure as it was used, and performance data for the method, have been published previously.⁷

STATISTICAL EVALUATION

The results were evaluated using non-parametric tests. Spearman's rank correlation coefficient was used to determine the degree and significance of association between two measurements; the significance of the differences between groups was determined with the Mann-Whitney U test.

Results

Faecal chymotrypsin concentrations in the two babies in AGA group who had necrotising enterocolitis were clearly different from the rest of the patients studied, and they are therefore considered separately.

BABIES WITHOUT EVIDENCE OF NECROTISING ENTEROCOLITIS

A total of 305 random stool specimens were obtained from the 19 preterm neonates without necrotising enterocolitis studied. For any individual patient, results showed a wide scatter over the four week period but only 22 (7%) specimens produced a result below the lower reference limit of 120 μg chymotrypsin/g stool previously determined for neonates greater than 36 weeks' gestation.¹⁰ Almost all of the low results occurred in the first few days of life with only one baby producing results below this limit after day 5.

BABIES WITH NECROTISING ENTEROCOLITIS

Fourteen (47%) of 30 results in the two babies who developed necrotising enterocolitis were below the lower reference limit of 120 μg chymotrypsin/g stool. One infant receiving breast milk had a low result on day 2, developed necrotising enterocolitis on day three of life, and was then intravenously fed until day 19. Results above 120 $\mu\text{g/g}$ stool were only seen from day 12 onwards. The second child was also fed with breast milk until signs of necrotising enterocolitis were noted on day 13, after which parenteral nutrition was given for six days. Daily stool chymotrypsin concentrations were below the lower reference limit up to day 5 and from days 8 to 13; concentrations were above the reference limit on day 6 (160 $\mu\text{g/g}$), day 7 (360 $\mu\text{g/g}$), and after day 14.

The random stool data from both the infants in the AGA and SGA groups (excluding the two babies with necrotising enterocolitis) were grouped into 24 hour periods (fig 1) and median values determined. The median concentration in babies in the AGA group increased steadily over the first week, reaching a peak value of 700 $\mu\text{g/g}$ stool by day 8, followed by a decline over the next two to three days, falling to 320 $\mu\text{g/g}$ stool by day 12. The median concentration in babies in the SGA group also increased over the

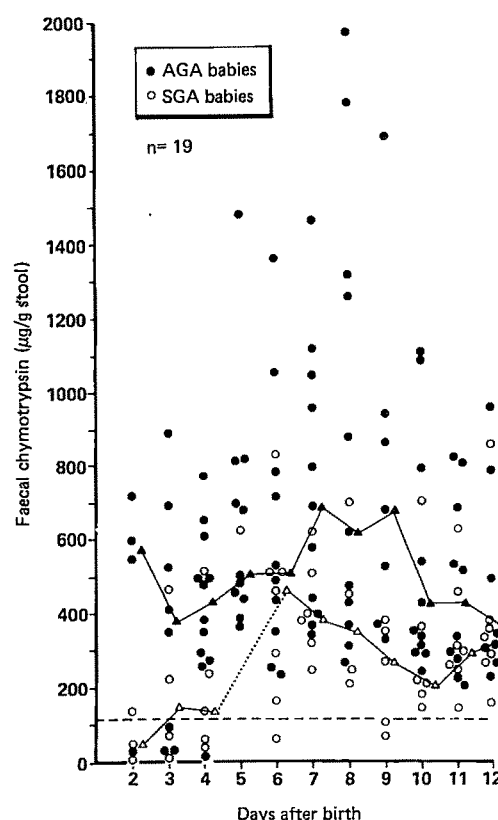


Figure 1 Association between faecal chymotrypsin and time from birth. Random stool chymotrypsin concentrations were grouped into 24 hour periods for days 2–12 from birth. The data from the two babies with necrotising enterocolitis were omitted. The median chymotrypsin concentrations (indicated by triangles) for each 24 hour period in infants in both the AGA and SGA groups are indicated by the continuous lines. The horizontal dashed line shows the lower limit of the observed range determined in 25 term babies.¹⁰

first week reaching a lower peak value of 470 $\mu\text{g/g}$ stool by day 6 followed by a decline and subsequent rise to 320 $\mu\text{g/g}$ stool by day 12. Faecal chymotrypsin concentrations on days 7 and 8 in infants in the AGA group were significantly higher than those on days 11 and 12. Faecal chymotrypsin concentrations on days 5 and 6 in infants in the SGA group were not significantly higher than those on days 11 and 12.

Median faecal chymotrypsin in relation to gestational age, birth weight, and intrauterine growth retardation

A median faecal chymotrypsin concentration was calculated for each baby using data from all stool specimens passed between day 2 and day 12 of life. The first day was not included because many of the most preterm infants opened their bowels for the first time on the second to the fourth day. The period day 2–12 was somewhat arbitrary and based on the observation that this interval encompassed the period of surge in faecal chymotrypsin and the fact that specimens were obtained for all babies up to day 12 but not thereafter due to transfer back to referring hospitals.

No correlation was found between median faecal chymotrypsin and gestational age ($r=0.28$, $p>0.05$). However, there was a significant positive correlation ($r=0.456$, $p<0.05$) between

median faecal chymotrypsin and birth weight (fig 2). Four babies in the SGA group had birth weights (880–1340 g) within the range of the 12 babies in the AGA group (800–2110 g), but they had significantly lower median chymotrypsin

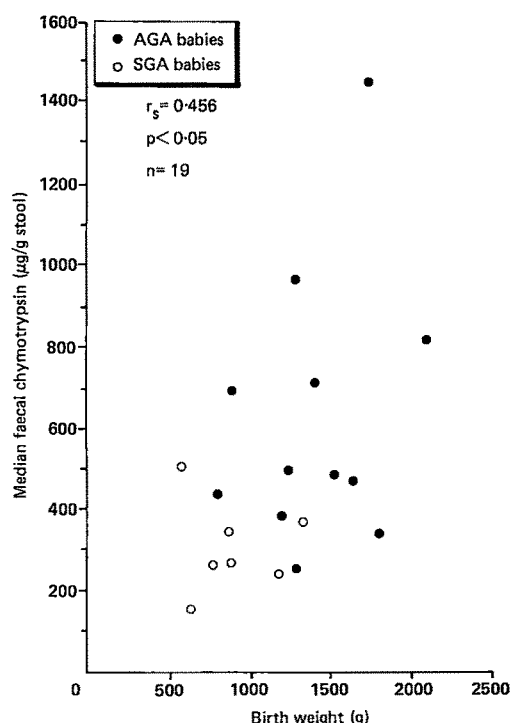


Figure 2 Correlation between faecal chymotrypsin and birth weight. Median faecal chymotrypsin concentrations were calculated for all babies for the period days 2–12 after birth. The median values showed a significant positive correlation with birth weight.

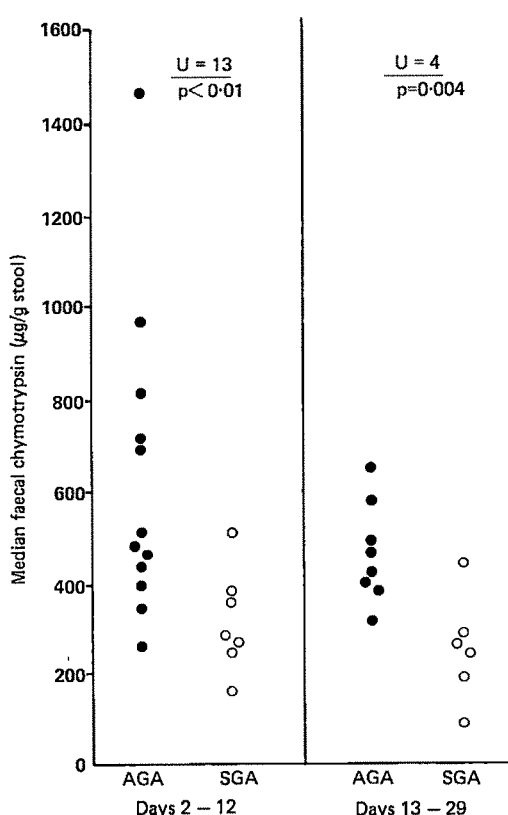


Figure 3 Comparison of faecal chymotrypsin concentrations in babies in the AGA and SGA groups for two periods from birth. Concentrations were significantly lower in the babies in the SGA group compared with those in the AGA group in both periods.

concentrations ($p=0.01$). When median chymotrypsin concentrations between 2 and 12 days in both groups of infants were compared, those in the SGA group were shown to have significantly lower values ($p<0.01$). Median concentrations calculated for the period 13–29 days (fig 3) showed that the differences between the two, now smaller, groups was sustained ($p=0.004$). Two babies who were partly parenterally fed had stool chymotrypsin values within the range observed for the rest of the group.

Discussion

The daily ranges of faecal chymotrypsin concentration determined in this study were similar to those described in term infants, only a few results falling below the term infant reference range¹⁰ during the first four days of life in the babies in the AGA group, and over the first nine days of life in those in the SGA group.

The daily median chymotrypsin concentration for both groups of babies increased steadily after birth reaching a peak at six days and eight days respectively. A similar peak has been reported in term infants but occurred at four days of age.¹⁰ As previously described in term babies a significant positive correlation ($r=0.456$, $p<0.05$) was found between birth weight and faecal chymotrypsin,¹⁰ with babies in the SGA group having significantly lower median chymotrypsin concentrations than those in the AGA group.

There is considerable uncertainty about the ontogeny of pancreatic exocrine function in the human neonate, with the principal enzymes each displaying a unique maturational pattern.¹¹ A previous intraduodenal study of pancreatic function indicated that the preterm neonate of 32 weeks' gestation or more has a significantly lower pancreatic enzyme secretion rate than the term infant.¹² Other workers, however, have claimed that enzyme secretion in preterm babies of greater than 32 weeks' gestation is the same as that at term,¹¹ and with respect to chymotrypsin at least, our results would support this.

Our study suggests that even premature babies from 23–32 weeks' gestation, a group not previously studied, secrete chymotrypsin in quantities similar to term babies, but may take a few days longer to fully establish secretory activity. Antonowicz and Lebenthal failed to detect enterokinase in postmortem fetal small bowel mucosa before 26 weeks' gestation,¹³ but our youngest subject with a gestational age of only 23 weeks showed faecal chymotrypsin concentrations within the reference range for term infants,¹⁰ indicating indirectly the presence of adequate enterokinase activity.

The surge seen in faecal chymotrypsin over the first few days of life has also been noted in intraduodenal studies of pancreatic exocrine function,¹² gastric acid secretion,¹⁴ and plasma gastrin and enteroglucagon.¹⁵ It is possible that the surge in chymotrypsin is a consequence of the secretion of regulatory peptides in response to food in the gut.¹⁶ Their effects may trigger a cascade of developmental changes including modulation of pancreatic exocrine function. The importance of enteral feeding in this

mechanism is indicated by the observation that surges in gastrointestinal hormones seen in preterm infants given bolus milk feeds were not seen in another group of infants who did not receive enteral feeds.¹⁶ Changes in hormone concentrations do not occur in infants who have never been fed.¹⁷ Deficient plasma clearance or the relatively large endocrine cell mass in the developing gut may explain why plasma concentrations of regulatory peptides reach much higher levels in preterm infants than adults. Such high concentrations may be necessary to induce receptor activity and the functional effects in target tissues.¹⁶

Two babies with subnormal faecal chymotrypsin measurements subsequently developed necrotising enterocolitis. The significance of this finding is uncertain, but suggests that impaired pancreatic proteolysis may be a contributory factor in the pathogenesis of necrotising enterocolitis. It is tempting here to draw an analogy with 'pig-bel', a fatal necrotising enterocolitis that occurs in the New Guinea highlands, when *Clostridium perfringens* infection coincides with the ingestion of large quantities of trypsin inhibitors in sweet potato.¹⁸ Alternatively, necrotising enterocolitis predates clinical symptoms, inhibiting pancreatic secretion while the baby is still apparently well.

The exocrine pancreas has a high rate of protein synthesis and it is not surprising that protein deprivation adversely affects function. Malnourished children have been shown to have severely reduced enzyme output with normal volume of secretions and bicarbonate output.¹⁹ Some children have shown little or no recovery of pancreatic exocrine function after nutritional repletion,²⁰ and malnutrition in childhood may result in irreversible pancreatic atrophy. Animal experiments have demonstrated that intrauterine growth retardation can also lead to impairment of pancreatic function. Studies on pregnant rats, for example, have shown that a reduction in uterine blood flow leads to decreased pancreatic weight and amylase and lipase content, but with unaffected concentrations of proteases in the rat pups.⁴ Similar findings have been reported in rat pups both from dams fed an inadequate diet during pregnancy²¹ and when malnourished in the early neonatal period.²² By showing that infants who are small for gestational age have significantly lower faecal chymotrypsin concentrations than infants of similar weight who are of appropriate size for gestational age, our study provides evidence for the first time that inadequate nutrition in utero may also have an adverse effect on pancreatic function in the human infant, which persists for at least the first four weeks of postnatal life. Although the

consequences of such an effect remain unknown, for the infant born with intrauterine growth retardation and faced with the necessity of catch up growth, it could represent a significant handicap and highlights the cardinal importance of appropriate nutrition.

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Submucous cleft palate in the differential diagnosis of feeding difficulties

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Abstract

Submucous cleft palate is a missed or forgotten diagnosis. We reviewed 81 patients with submucous cleft palate seen over a 15 year period; 26 of these patients were interviewed. The patients were divided into three main groups according to the referral pattern. Children under 2.5 years were referred by a paediatrician for feeding problems; children aged 2.5-10 were referred mainly by speech therapists; and those over 10 had a varied pattern of referral. Thirty nine of the 81 had problems with feeding, but of the 26 interviewed, 22 had feeding problems.

Not all patients with a submucous cleft palate are symptomatic and require active treatment, but children with this condition have the same high incidence of middle ear disease as those with overt cleft palate. We suggest that the diagnosis of submucous cleft palate be included in the differential diagnosis of feeding difficulties, with early referral to a specialist cleft palate team.

Submucous cleft palate is a forgotten or missed diagnosis and can be defined as the abnormal attachments of the palatal muscles with intact oral and nasal mucosa.^{1,2} This can therefore result not only in feeding and speech difficulties but also eustachian tube dysfunction with middle ear disease.³

The incidence of the condition is said to be one in 1200,³ with a 4% incidence in a cleft lip and palate clinic population.⁴

The diagnosis of submucous cleft palate can be made on the classical triad of signs: that is, a bifid uvula, a translucent zone in the midline of the soft palate, and an absent or notched posterior nasal spine. These signs are not always evident, however,^{1,5} but must still be looked for. An isolated bifid uvula can occur in 0.1-3% of the normal population.² If the diagnosis is suspected the most reliable means of confirming it is barium coated videofluoroscopy and nasopharyngoscopy, where practical.^{1,2} This will confirm the loss of the normal musculus uvulae ridge on the nasal surface with the resulting valley in the midline, as also seen in the poorly repaired overt cleft palate patient. Should there be any indication for surgery, the muscles of the palate can be explored, the abnormal attachments confirmed, and then reconstructed in their normal position to create the levator sling.

Only 10% of cases of submucous cleft palate are symptomatic,³ but it is important that these patients are diagnosed to allow full assessment

of middle ear function and speech as early treatment, if required, achieves the best results.⁶ The incidence of middle ear disease (recurrent infective otitis media or chronic secretory otitis media, or both) is as high as in the overt cleft palate, that is between 59-93%.² In view of this the indications for adenoidectomy for repeated middle ear symptoms in these patients must be questioned as the cause of these symptoms may be due to the abnormal muscle attachments, and adenoidectomy may not improve the incidence of middle ear disease. Adenoidectomy may make a borderline velopharyngeal sufficiency into appreciable insufficiency requiring investigations and possible surgery.^{7,8} Another reason for avoiding adenoidectomy generally is that even with a normally functioning palate the pharynx may be relatively large (velopharyngeal disproportion), and nasal escape may result.^{9,10}

Patients and methods

A review of the history, signs, symptoms, and referral patterns of patients with the diagnosis of submucous cleft palate first seen between 1972-87 was undertaken. The notes and video recordings were reviewed, and in addition, as many patients and parents as could attend were interviewed by a speech therapist and reconstructive plastic surgeon.

The patients were divided into age groups as follows: 0-2.5 years (2.5 years tends to be the earliest an experienced speech therapist can assess speech), 2.5-5 years (5 years of age is when many children start school and any difficulties in the production of speech sounds are established), 5-10 years, 10-15 years, 15-20 years, and over 20 years. For clarity and simplifications of the tables, the groups have been amalgamated according to their referral pattern.

Results

The details of 81 patients with a proved submucous cleft palate were reviewed, although only 26 patients were available to be interviewed. There appeared to be three patterns of referrals (table 1) with those under 2.5 years (in fact under 18 months) being referred by a paediatrician with feeding problems (longer than 40 minutes to feed and nasal regurgitation). The feeding improved with surgery but seven out of nine children subsequently developed middle ear symptoms. This may reflect the natural history of chronic secretory otitis media in the normal population.

The second group were the children between 2.5-10 years where 46 out of 56 were referred

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Table 1 Referral pattern of patients with a submucous cleft palate to a cleft lip and palate clinic

Age group (years)	Speech therapist	Ear, nose, and throat surgeon	Paediatrician	General practitioner	Oral surgeon	Orthodontist	School medical officer	Psychiatrist	Unknown	Total patients
<2.5			9							9
2.5-10	29	17	3	3		1	1		2	56
>10	3	5		2	3	1	1	1		16
Total patients	32	22	12	5	3	2	2	1	2	81

Table 2 Incidence of the main symptoms associated with submucous cleft palate in the three groups

Age group (years)	Problems with:			Total
	Speech	Ears	Feeding	
<2.5	—	7	9	9
2.5-10	56	40	23	56
>10	16	5	7	16
Total	72	52	39	81

by speech therapists or ear, nose, and throat specialists for speech difficulties; 40 of this group had middle ear pathology (table 2). Twenty three of these 56 children had a positive history of feeding difficulties as a baby; the incidence may be a higher as this aspect is not always documented.

The last group were over 10 years of age where there was a diffuse pattern of referral, although all had speech problems. Seven out of 16 had a history of feeding difficulties as a baby but again the incidence may be higher.

Of the 26 patients and parents interviewed, 22 gave a positive history of slowness to feed and nasal regurgitation; the other four could not remember.

Discussion

There is very little written, even in standard textbooks, about normal variables of feeding in neonates, although the physiology of suck and swallowing is well documented.¹¹⁻¹⁵ Feeding should take five to 20 minutes with half in the first two minutes and 80-90% completed by four minutes.^{15 16} A more recent study has shown a wider range of feeding times for normal breast fed babies (four to 23 minutes) with an average of 54-58% of the intake achieved by four minutes.¹⁷ The more common yardstick as to normal feeding is the baby's ability to maintain and increase his weight, however long it takes.¹⁸ This is not always practical, however, as 13% of mothers give up breast feeding in the first two weeks because 'feeding takes too long and is too tiring'.¹⁹ Others have defined slowness to feed as taking longer than 30 minutes.¹³ We have defined 'slowness to feed' as taking longer than 40 minutes.

Little is mentioned of 'feeding difficulties' in the normal population. There are many causes of 'slowness to feed', however, including respiratory, cardiovascular, renal, infective, neurogenic, and myopathic.^{11-14 18} Cleft lip or overt cleft palate, or both, are well known causes of problems with feeding but 'Cleft palates may be

small and submucous or extensive and associated with considerable nasal regurgitation and choking during feeds'¹¹ or 'rarely cause problems, but in severe defects sucking and swallowing may be difficult'.¹³ There is even less written about 'nasal regurgitation', which should be defined as the emission of fluid out of the nose during peaceful feeding (to differentiate from vomiting). The only causes of this are overt clefting of the palate or neuromuscular incoordination of the velopharynx (for example, suprabulbar palsy).^{11 12 18} There appears to be no mention of submucous cleft palate as a cause of this symptom. As nasal regurgitation is a form of velopharyngeal insufficiency,¹⁴ which is usually associated with speech abnormalities, it is not surprising that feeding problems are directly related to subsequent difficulties in speech development.²⁰ Therefore the combination of slowness to feed and nasal regurgitation in the neonate or baby should alert the midwife, health visitor, obstetrician, and neonatologist to the possibility of a submucous cleft palate being present.

The examination of the neonate is not always explicit in advocating palpation of the roof of the mouth with the tip of the little finger, but suggests that 'the soft and hard palate should be inspected for a hidden cleft'.²¹ Absence or notching of the posterior nasal spine is the most commonly present of the three classical signs,^{1 4 5}, although the absence of signs should not prevent the diagnosis of submucous cleft palate being considered. If the condition is suspected, an early referral to a cleft lip and palate clinic is indicated.

It is unfortunate that more paediatricians are not regularly involved in cleft lip and palate clinics as more research into feeding, speech, and eustachian tube function would result in better understanding of these complex mechanisms and allow us to tailor the treatment to the specific anatomical and physiological problem.^{1 2 9 10 22}

In conclusion it is suggested that the combination of a 'slowness to feed' (>40 minutes) and 'nasal regurgitation' (velopharyngeal insufficiency) is strongly suggestive of a submucous cleft palate, assuming there is no other obvious cause of these symptoms. It is also suggested that those babies with feeding difficulties as a result of a submucous cleft palate will stand a high chance of developing middle ear disease as well as significant nasal escape and should therefore be kept under regular review by a 'cleft palate team'. Adenoidectomy should be avoided in this group even if the patients appear to have acceptable speech as speech could deteriorate after the procedure.

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Factors influencing the presence of faecal lactobacilli in early infancy

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Abstract

The faecal flora of 46 preterm infants and 52 born at full term was studied at 10 days of age; 46 born at full term and 37 preterm infants were also studied at 30 days. Viable counts of coliforms, lactobacilli, and bifidobacteria were made; gas liquid chromatography was used to identify the anaerobes. Lactobacilli, but not bifidobacteria, were found in high counts in the stools of most of the infants born at full term by 30 days of age. The mode of delivery, but not the method of feeding, had a significant influence on early colonisation. A selective deficiency of lactobacilli compared with coliform organisms was found in preterm infants. Previous treatment with antibiotics and being nursed in an incubator were also significantly associated with a lower rate of early colonisation with lactobacilli. Our findings indicate that lactobacilli may be an important part of the normal stool flora in early infancy, and that modern methods of neonatal care are associated with delayed or deficient colonisation.

There has recently been a resurgence of interest in the bacterial content of the stool of newborn infants, particularly that of preterm infants. It has been suggested that preterm neonates may benefit from being given lactobacilli orally,¹ though one recent study failed to show any advantage to infants so treated.² Other workers have used antibiotics given orally to adults in an attempt to induce a favourable bowel flora and thus promote 'colonisation resistance'.³

Although studies have been carried out in many parts of the world, the normal pattern of bacterial colonisation of the stool may be more complex than previously reported.⁴ In particular, earlier studies almost unanimously reported an overwhelming predominance of bifidobacteria in the stool of infants born at full term who were breast fed,⁵⁻⁷ but two recent studies using the more specific technique of gas liquid chromatography for anaerobe identification, indicated that neither bifidobacteria nor lactobacilli were predominant in most normal infants born at full term, whether they were breast fed or bottle fed.^{8,9}

Before the possibility of influencing the bowel flora of preterm infants is seriously considered, it is advisable to determine—using modern techniques of identification of organisms—whether a characteristic pattern of colonisation with lactobacilli and bifidobacteria can be identified in infants born at full term, and in preterm infants.

Subjects and methods

INFANTS BORN AT FULL TERM

Infants were recruited into the study within the first few days of life after informed parental consent had been obtained. In order to investigate the effect of mode of delivery and method of feeding, the study was designed to recruit roughly equal numbers of babies in the following four categories: vaginal delivery and breast fed, vaginal delivery and bottle fed, caesarean section and breast fed, and caesarean section and bottle fed.

The infants were either exclusively breast fed or bottle fed on cows' milk formula. Infants were excluded if they were treated with antibiotics or, in the case of infants who were breast fed, their mothers received antibiotic treatment. Of the 52 babies studied at 10 days, seven were excluded at 30 days: three had changed from breast to bottle feeding, two did not pass stools between 28 and 32 days, one had been prescribed antibiotics, and the mother of one infant being breast fed had been taking antibiotics. Forty five infants were studied at both 10 and 30 days of age. One infant was studied at 30 days only because no stool was passed between 8 and 12 days. None of the babies studied had been admitted to the special care baby unit. Clinical details are shown in table 1.

PRETERM INFANTS

All infants were born at 33 weeks' gestation or less, and all were in the special care baby unit when specimens were collected. None of the infants had received any antibiotics for at least 48 hours before collection. All infants were receiving enteral feeds, either expressed breast milk, pooled pasteurised breast milk, artificial milk, or a combination of breast and artificial milk. Infants were described as being nursed in a cot if they had been in open cots for at least 48 hours. Twenty infants were studied at 10 and 30 days. Clinical details of the preterm infants are shown in table 2.

Preliminary studies indicated that the faecal

Table 1 Clinical details of infants born at full term

	At 10 days of age (n=52)	At 30 days of age (n=46)
Median (range) birth weight (g)	3240 (2300-4320)	3350 (2300-4320)
Median (range) gestational age (weeks)	40 (38-42)	40 (38-42)
Born by vaginal delivery:		
Breast fed	15	13
Formula fed	12	12
Born by caesarean section:		
Breast fed	15	11
Formula fed	10	10

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Table 2 Clinical details of preterm infants

	At 10 days of age (n=42)	At 30 days of age (n=37)
Median (range) birth weight (g)	1440 (620-2510)	1200 (620-2440)
Median (range) gestational age (weeks)	32 (25-33)	30 (25-33)
Vaginal delivery	18	18
Caesarean section	24	19
No (%) treated with antibiotics	30 (71)	32 (86)
No (%) nursed in incubator	36 (86)	20 (54)

flora is well established after the first week of life, and significant changes are unusual after 1 month of age. We decided, therefore, to collect our samples at 10 days (range 8-12) and at 30 days (range 28-32).

SAMPLE COLLECTION

A written explanation of how to collect the specimen was given to the parents of the infants born at full term. Approximately 1 g of stool was collected as soon as possible after voiding and immediately placed in a bottle of transport medium. This was then put in a domestic refrigerator or cool environment until processing.

Transport medium

Several criteria had to be met for the successful transport of infant faecal samples. Firstly, the medium had to be sufficiently viscous to prevent spillage when the bottle was opened, as it was weighed before collection of the sample and weighed again when the sample had been added. Secondly, it had to be sufficiently fluid to allow thorough mixing of the sample with the medium. Thirdly, the medium had to be clear so that the mothers could see how big a sample they had collected. Finally, the medium had to protect the bacteria being studied and keep them viable without proliferation between collection and processing. The medium selected was a buffered salt solution—Cary-Blair medium (Oxoid)—with only half the normal amount of agar. This allowed the sample to be kept for up to seven days at 4°C with little alteration to the components of the flora being studied. In practice samples were plated within three days of collection.

ISOLATION AND ENUMERATION OF BACTERIA

Coliforms were cultured using McConkey's agar (Oxoid No 3 CM115); for lactobacilli, acetate agar was used¹⁰ and for bifidobacteria we developed a medium based on that of deMan *et al*¹¹ (without the acetate, as this interferes with

the subsequent gas liquid chromatography), but with the addition of cysteine (0.05%); raffinose, fructose, and galactose (0.05% each); 70 µg/ml neomycin, and 0.05 µg/ml rifampicin. Serial dilutions of the above media were made in sterile 1/4 strength Ringer's salt solution, 1 ml of the appropriate dilution being incorporated in pour plates of the media. The viable count was expressed as the log₁₀ of colony forming units/g wet weight of faeces. Other methods of differentiation of lactobacilli and bifidobacteria used included analytical profile identification strips, and gas liquid chromatography of bacterial metabolites.¹²

Previous work using known strains had established that there was a clear difference between the amount of acetic acid produced by lactobacilli and that produced by bifidobacteria.¹²

The methods allowed bacteria to be identified in counts of at least 10³ g for coliform organisms, 10⁴ g for lactobacilli, and 10⁷ g for bifidobacteria.

STATISTICAL METHODS

The χ^2 test was used to assess the significance of differences between the numbers of infants colonised, and the Mann-Whitney U test was used to compare bacterial counts between groups. For analysis of smaller numbers Fisher's exact test was used.

The study received the approval of the joint ethics subcommittee of the Southampton and South West Area Health Authority, and the University of Southampton.

Results

INFANTS BORN AT FULL TERM

Tables 3 and 4 show the number of infants colonised and the median counts for the three organisms at 10 and 30 days, respectively, for mode of delivery and type of feeding.

Coliform organisms were present in most infants at both 10 and 30 days of age, and bifidobacteria were detected in a few, lactobacilli were present in most of the infants by 30 days of age. Colonisation with lactobacilli at 10 days was significantly associated with delivery by the vaginal route ($p < 0.03$), but there was no significant difference in the median counts of lactobacilli. Mode of delivery did not seem to have an appreciable influence on bacterial counts or on colonisation at 30 days. There was no significant difference between median counts or the proportion of infants colonised when breast and bottle fed infants were compared at either 10 or 30 days of age. Fifteen of the formula fed infants were receiving SMA

Table 3 Colonisation at 10 days in infants born at full term

	Coliforms		Lactobacilli		Bifidobacteria	
	No (%) colonised	Median log ₁₀ count/g wet weight of faeces	No (%) colonised	Median log ₁₀ count/g wet weight of faeces	No (%) colonised	Median log ₁₀ count/g wet weight of faeces
All infants born at full term (n=52)	46 (88)	8.82	23 (44)	8.56	11 (21)	10.09
Breast fed (n=30)	26 (87)	8.72	13 (43)	7.89	8 (27)	10.24
Bottle fed (n=22)	20 (91)	8.92	10 (45)	8.69	3 (14)	10.01
Vaginal delivery (n=27)	24 (89)	8.85	16 (59)*	8.56	8 (30)	10.00
Caesarean section (n=25)	22 (88)	8.80	7 (28)*	8.19	3 (12)	10.39

* $p < 0.03$. Only positive samples were used to calculate the median values.

Table 4 Colonisation at 30 days in infants born at full term

	Coliforms		Lactobacilli		Bifidobacteria	
	No (%) colonised	Median log ₁₀ count/g wet weight of faeces	No (%) colonised	Median log ₁₀ count/g wet weight of faeces	No (%) colonised	Median log ₁₀ count/g wet weight of faeces
All infants born at full term (n=46)	46 (100)	8.70	29 (63)	8.95	6 (13)	9.71
Breast fed (n=24)	24 (100)	8.65	14 (58)	8.77	5 (21)	9.48
Bottle fed (n=22)	22 (100)	8.73	15 (68)	9.11	1 (5)	10.30
Vaginal delivery (n=25)	25 (100)	8.55	17 (68)	9.05	4 (16)	9.40
Caesarean section (n=21)	21 (100)	9.04	12 (57)	8.21	2 (10)	10.12

Only positive samples were used to calculate the median values.

(Wyeth) at both 10 and 30 days; of the remainder, two were receiving Aptamil (Milupa), two were receiving Osterfeed (Farley), and three were receiving Cow and Gate Premium. In comparing the infants fed with SMA and those fed on other formula feeds, no difference in the pattern of colonisation was found at either 10 or 30 days of age.

COMPARISON OF INFANTS BORN AT FULL TERM AND PRETERM INFANTS

In comparing the two groups, at 10 days the prevalence of colonisation was significantly lower in the preterm group for both coliform organisms ($p < 0.01$) and lactobacilli ($p < 0.005$), but once again no difference in median counts was seen among those infants who were colonised. At 30 days, although almost all the infants were colonised with coliforms, there was still a highly significant difference in the rates of colonisation with lactobacilli ($p < 0.001$).

PRETERM INFANTS

Tables 5 and 6 show the results for the preterm

infants studied at 10 and 30 days of age, respectively, for mode of delivery, environment in which they were nursed, and whether they had been treated with antibiotics.

Although there was no significant difference in either prevalence of colonisation or median bacterial counts when modes of delivery were compared, the trends were similar to those seen among infants born at full term.

Of the six infants nursed in open cots at 10 days of age, two had been in cots for two days, one for four days, two for six days, and one for 10 days. Of the 17 infants nursed in open cots at 30 days of age, 15 had been in cots for seven days or more. There was a highly significant difference at 10 days in the prevalence of colonisation by lactobacilli of infants who were nursed in incubators compared with those in open cots ($p < 0.001$). There was no difference in colonisation by coliform organisms, and no difference was found at 30 days. At 10 days those infants who had previously been treated with parenteral antibiotics had significantly reduced colonisation rates of lactobacilli ($p < 0.01$). No difference in colonisation with

Table 5 Colonisation at 10 days in preterm infants

	Coliforms		Lactobacilli		Bifidobacteria	
	No (%) colonised	Median log ₁₀ count/g wet weight of faeces	No (%) colonised	Median log ₁₀ count/g wet weight of faeces	No (%) colonised	Median log ₁₀ count/g wet weight of faeces
All preterm infants (n=42)	26 (62)	8.45	6 (14)	7.72	3 (7)	8.98
Vaginal delivery (n=18)	14 (78)	7.55	5 (28)	7.84	3 (17)	8.98
Caesarean section (n=24)	12 (50)	8.58	1 (4)	7.60	0	0
Treated with antibiotics (n=30)	19 (63)	8.65	2 (7)*	8.22	1 (3)	9.48
Not treated with antibiotics (n=12)	7 (58)	6.80	4 (33)*	7.72	2 (17)	8.90
Nursed in incubator (n=36)	22 (61)	8.50	3 (8)**	7.60	1 (3)	8.83
Nursed in cot (n=6)	4 (67)	7.50	3 (50)**	7.84	2 (33)	9.23

* $p < 0.01$; ** $p < 0.001$. Only positive samples were used to calculate the median values.

Table 6 Colonisation at 30 days in preterm infants

	Coliforms		Lactobacilli		Bifidobacteria	
	No (%) colonised	Median log ₁₀ count/g wet weight of faeces	No (%) colonised	Median log ₁₀ count/g wet weight of faeces	No (%) colonised	Median log ₁₀ count/g wet weight of faeces
All preterm infants (n=37)	35 (95)	8.90	7 (19)	7.18	4 (11)	9.18
Vaginal delivery (n=18)	17 (94)	8.90	3 (17)	8.01	1 (6)	8.95
Caesarean section (n=19)	18 (95)	8.88	4 (21)	6.89	3 (16)	9.41
Treated with antibiotics (n=32)	30 (94)	8.82	7 (22)	7.18	4 (12)	9.18
Not treated with antibiotics (n=5)	5 (100)	9.39	0	0	0	0
Nursed in incubator (n=20)	18 (90)	8.82	3 (15)	6.84	2 (10)	8.97
Nursed in cot (n=17)	17 (100)	8.91	4 (24)	7.59	2 (12)	9.18

Only positive samples were used to calculate the median values.

either coliforms or lactobacilli was found at 30 days.

Of the 36 infants who were nursed in incubators at 10 days of age, 27 had previously received treatment with antibiotics, as had three of the six infants nursed in open cots at 10 days. Because of the small number of infants who had not received treatment with antibiotics it was not possible to distinguish whether the place they were nursed or the antibiotics exerted the greater influence on early bacterial colonisation.

At 10 days, 23 of the preterm infants received expressed breast milk (a mixture of maternal and donor breast milk) only, five received a mixture of expressed breast milk and formula feed, and 14 received formula feed only. No difference in the pattern of bacterial colonisation was found among these three groups of infants, and no difference was found when the types of formula feed were compared. At 30 days of age nine infants received expressed breast milk from their own mothers, 11 received a mixture of expressed breast milk and formula feed, and 17 were fed with formula feed alone. Again no differences in the pattern of bacterial colonisation were found when types of feeding were compared.

Discussion

The results indicated that in most of these babies bifidobacteria were not usually found in the faeces. When they were detected, however, they were present in large numbers. Our findings are at variance with those of many previous studies,^{5-7 13} and though it is possible that some of the earlier reports may have failed to discriminate between lactobacilli and bifidobacteria because of less precise microbiological identification methods, this is not likely to have been the case in those more recent studies that used gas liquid chromatography for the identification of bacteria.^{14 15}

In addition, we were unable to confirm an inverse relationship between counts of bifidobacteria and lactobacilli, and coliform organisms, in contrast to some previous reports.^{16 17} In view of the high counts of coliforms that we found, differences in methods are unlikely to account for this disparity and it is possible that there has been a change in the nature of early faecal colonisation in infants born in industrialised countries, an explanation that is supported by the findings of at least two recent studies.^{8 9} There could be many reasons for such a change, ranging from differences in maternal dietary habits to changing obstetric practices, particularly regarding the use of vaginal antiseptics at the time of birth. Only one of the breast feeding mothers in our study used a nipple antiseptic preparation and this practice is unlikely, therefore, to have been an important factor in any ecological changes in colonisation with bifidobacteria.

The use of gas liquid chromatography for identification of bacteria allows us to state with confidence that lactobacilli were present in appreciable numbers in most of the infants born at full term by 30 days of age. In contrast to the many previous studies that have shown an asso-

ciation between colonisation with bifidobacteria and breast feeding, our findings indicate that the method of feeding was not related to colonisation with lactobacilli.

In our study there was, however, a significant difference when mode of delivery was considered, infants born at full term by the vaginal route being more likely to acquire lactobacilli by 10 days of age. It is possible, therefore, that an important contribution to the lactobacillary flora is acquired from the birth canal. No such relationship was found at 30 days, however, and it is likely that lactobacilli are also acquired from other sources during the first few weeks of life.

Although one study about the administration of lactobacilli to preterm infants has been published,² and at least one other group in the United States is actively concerned in preparing such a trial,¹ there have been few published reports before this to suggest that lactobacilli form an important part of the faecal flora of newborn infants. These findings, and those of other workers, indicate that factors such as prematurity, birth by caesarean section, parenteral antibiotic treatment, and being nursed in an incubator, may deprive infants of colonisation with lactobacilli during the first few days, and even weeks, of life.¹⁵ It is not yet clear whether this deficiency is to the detriment of the infants.

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Helicobacter pylori in Gambian children with chronic diarrhoea and malnutrition

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Abstract

Infection with *Helicobacter pylori* (formerly *Campylobacter pylori*) was studied by measuring antibody titres to *H pylori* in Gambian children. Serological evidence of infection was found in 12 of 82 (15%) infants aged less than 20 months; this increased to 62 of 135 (46%) in those aged 40-60 months. Positive serology was found in 41 of 77 (53%) infants with chronic diarrhoea and malnutrition (mean age 19 months, range 5-36) compared with 18 of 70 (26%) of age matched healthy controls and nearly a quarter (12/49, 24%) of age matched undernourished (marasmic) subjects. These data show that infection with *H pylori* is common in the Gambia and that in infancy this infection is associated with chronic diarrhoea and malnutrition.

Chronic diarrhoea and associated malnutrition is a major cause of childhood morbidity and mortality in developing countries. The pathogenesis of chronic diarrhoea and malnutrition is multifactorial,¹ and it is often associated with infection of the gastrointestinal tract. In a small percentage of affected infants pathogenic bacteria such as *Shigella* spp, *Salmonella* spp and enteropathogenic *Escherichia coli* are found.² More often micro-organisms of uncertain pathogenicity such as *Giardia lamblia* are identified.^{3,4} Finally in most cases of well established chronic diarrhoea and malnutrition the small intestine contains high concentrations of colonic bacteria, which contribute to small intestinal dysfunction.^{5,6}

The first major host defence against small bowel contamination, the gastric acid barrier,^{7,8} may be compromised in children with protein energy malnutrition. Gracey *et al* described gastritis and achlorhydria in eight out of nine patients with protein energy malnutrition and, although the cause of the gastritis was not established, it was attributed, in part, to high bacterial counts found in the gastric contents.⁹

Infection with *Helicobacter pylori* (formerly *Campylobacter pylori*) seems a likely aetiological agent. This organism causes an active chronic gastritis and,¹⁰ furthermore, it has become clear that *H pylori* gastritis may be associated with a rise of fasting gastric pH.¹¹⁻¹³ Diminished gastric acid output has persisted more than a year in several cases.¹⁴ *H pylori* is found in adult populations around the world,^{15,16} but is uncommon in children in the Western world.¹⁷ The link between *H pylori* infection, achlorhydric gastritis, and bacterial overgrowth in the small intestine in children with chronic diarrhoea and malnutrition has not been investigated.

The aims of the study described in this paper were twofold: (1) to measure antibody titres to *H pylori* in Gambian patients with *H pylori* associated with gastritis, that had been proved histologically, so as to define antibody titres diagnostic of infection, and (2) to use serology to determine the prevalence of *H pylori* infection in Gambian children with chronic diarrhoea and malnutrition and in controls.

Subjects and methods

VALIDATION OF SEROLOGICAL METHOD OF DIAGNOSING CHRONIC INFECTION WITH *H PYLORI*
Fifty six subjects were examined for *H pylori* infection: 36 were adults referred because of a long history of dyspepsia (16 men, 20 women, mean age 34.7 years) and 20 were children. Of the children 17 had chronic diarrhoea and malnutrition, one had toddler diarrhoea, one (aged 9 years) had chronic dyspepsia, and one had recurrent respiratory infections and marasmus. Gastrosocopy was performed on these subjects (method in infants as described previously¹⁸) and four biopsy specimens of antral mucosa were taken. Two specimens were put in sterile phosphate buffered saline for microbiological culture and two were fixed in buffered formalin solution for histological examination.

Specific anti-*H pylori* IgG was measured by enzyme linked immunoabsorbent assay (ELISA).¹⁹ The antigen was prepared from whole organisms, using strains from the National Collection of Type Cultures (NCTC) (11637 and 11916), and strains of organisms isolated from individuals in The Gambia. Test sera were run on plates with a standard calibration serum derived from pooled *H pylori* positive sera from children in the United Kingdom. This serum was given an arbitrary ELISA value of 100 ELISA units. A calibration curve was constructed for each plate to allow each test serum to be given an ELISA value relative to the calibration serum. Each plate also had serial dilutions of a known negative control serum.

PREVALENCE OF ANTIBODIES TO *H PYLORI* IN A RURAL GAMBIAN POPULATION

Stored sera from 361 children aged less than 5 years resident in villages near the town of Farafenni on the north bank of The Gambia river were available for study. These sera were obtained during a malaria survey undertaken in November 1986 and represented each child

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Table 1 Details of children with chronic diarrhoea and malnutrition and two control groups: well and malnourished

Group	Age (months)		Sex (M/F)	No with marasmus/ marasmic-Kwashiorkor	Weight for height†	
	Mean (SD)	Range			Mean (SD)	Range
Chronic diarrhoea and malnutrition (n=77)	19.0 (6.3)	5-36	40/37	55/22	65.1 (7.9)	47-90
Well (n=70)	18.3 (8.6)	6-36	40/30	—	95.7 (3.7)	92-103
Malnourished* (n=49)	19.4 (7.7)	6-35	25/24	29/0	67.2 (4.9)	58-74

*These children had protein energy malnutrition.

†% NCHS median.

from every fifth compound in their respective villages. Basic demographic and anthropometric data were collected during the survey.

PREVALENCE OF ANTIBODIES TO *H PYLORI* IN CHILDREN WITH CHRONIC DIARRHOEA AND MALNUTRITION

Samples of sera were obtained from three groups of children: 77 with chronic diarrhoea and malnutrition; 70 asymptomatic well nourished children (weight for height >90% National Center for Health Statistics (NCHS) median value), and 49 malnourished children without diarrhoea (table 1). Chronic diarrhoea was defined as diarrhoea with more than three loose stools/day for more than two weeks and protein energy malnutrition when the weight for height fell below 75% of the NCHS median value. In patients with chronic diarrhoea and malnutrition the mean duration of diarrhoea was 12 weeks (range two to 52 weeks). The three groups were well matched for age and sex.

Marasmic control patients were recruited from the ward and outpatient department at the Medical Research Council (MRC) hospital in Fajara, and healthy controls were obtained with the help of field workers from the adjacent township of Bakau and from rural villages around Farafenni. Similar proportions of the groups of marasmic and healthy control children came from either a rural or an urban environment. *H pylori* infection was determined serologically and its prevalence in the three groups compared.

The protocol for the study was approved by the committee on human experimentation of the MRC Laboratories in The Gambia. Statistical analysis was performed by the χ^2 test and the *t* test where appropriate.

Results

ANTIBODIES TO *H PYLORI* IN PATIENTS UNDERGOING ENDOSCOPY

Antibodies to *H pylori* were measured in 36 adults and in 20 children who underwent gastrointestinal endoscopy. Satisfactory antral biopsies were obtained from 34 adult patients; 33 had antral gastritis. *H pylori* was identified in 32 patients by examination of Giemsa stained tissue sections (32/34) and Gram stained wet preparations (28/34). The organism was grown in pure culture from three patients. No bacteria were identified on the mucosa of the one patient with normal histology. Titres of specific anti-*H pylori* (NCTC) IgG were greater than 100 ELISA units in all adult patients in whom *H pylori* were identified. Similar results were obtained with antigens prepared from the

NCTC strain of *H pylori* and the Gambian isolates. A similar association between raised antibody titres to *H pylori* and the demonstration of the bacterium on gastric mucosa was found in children. Sixteen of the 20 children endoscoped had antral gastritis. Eleven children had *H pylori* on their antral mucosa. Circulating IgG antibodies against *H pylori* were found in 13 children all of whom had antral gastritis (*H pylori* identified histologically in eight). They were not found in seven children: including all four with a histologically normal antral mucosa, two with atrophic gastritis but without *H pylori*, and in only one with gastritis and *H pylori* (table 2).

The titre of circulating antibodies exceeded 100 ELISA units in all adults and in eight out of the 13 children in whom *H pylori* was identified. In the remaining five infants the titre was more than 40 ELISA units dilution. Based on these findings in adults and children we concluded that an antibody titre of 100 ELISA units or greater strongly suggests an active infection with *H pylori*.

ANTIBODIES TO *H PYLORI* IN GAMBIAN VILLAGE CHILDREN

The prevalence of antibodies to *H pylori* at a titre of 100 ELISA units or greater in Gambian village children is shown in table 3. The prevalence of a raised antibody titre increased from 15% (12/82) children aged 0-19 months, to 27% (37/136) of those aged 20-39 months, and to 46% (62/135) in those children aged 40-60 months. Anthropometric data was available on these children and in those below 30 months of age there was a significant effect of malnutrition on the prevalence of high anti-*H pylori* antibody

Table 2 Correlation of anti-*H pylori* IgG with histological findings in gastric mucosa (n=20)

	<i>H pylori</i> present	<i>H pylori</i> absent
Antral gastritis (n=16)	9	7
Antibody titre (ELISA units):		
>100	8	—
10-100	—	5
Negative	1	2
No antral inflammation (n=4)*	2	2

*All four were negative on ELISA.

Table 3 Age related prevalence of anti-*H pylori* antibody titres

Age range (months)	Specific IgG titre >100 ELISA units (% prevalence)
0-19	12/82 (15)
20-39	37/136 (27)
40-60	62/135 (46)

titres. In this group 11 of 39 (28%) of those with marasmus (weight for height <75% NCHS median value) had antibody titres of 100 ELISA units or more compared with only 14 of 116 (12%) of those in the same age group who were well nourished ($\chi^2=4.488$, 1 df, $p<0.03$). This effect of malnutrition was not seen in the children over 30 months of age.

ANTIBODIES TO *H. PYLORI* IN CHILDREN WITH CHRONIC DIARRHOEA AND MALNUTRITION AND CONTROLS

Antibodies to *H. pylori* at a titre of 100 ELISA units or greater were found significantly more frequently in children with chronic diarrhoea and marasmus (41/77, 53%) than in children with marasmus but no diarrhoea (12/49, 24%) or than in healthy age matched control children (18/70, 26%) ($\chi^2=9.0$, 1 df, $p<0.01$ and $\chi^2=10.5$, 1 df, $p<0.01$ respectively). Seventeen of the children with chronic diarrhoea and malnutrition also underwent endoscopy. *H. pylori* was demonstrated on the mucosa of 10 of these children.

Discussion

In this study we have shown the value of the serological diagnosis of *H. pylori* in the community under study and demonstrated that infection of the gastric mucosa with *H. pylori* is established early in life in many children in The Gambia. The high anti-*H. pylori* antibody titres found in The Gambia may reflect chronic infection and therefore prolonged antigenic stimulation. In a random population antibodies were found in 46% of children aged 40–60 months. In Britain the prevalence of infection in this age group is unknown but preliminary data from Newcastle suggests that it is around 1% and less than 6% for the age group 5–16 years.¹⁷ The route of acquisition of *H. pylori* infection is not yet established, but it is possible that person to person contact is involved.^{20–22} Living conditions in The Gambia and especially feeding practices whereby children eat by hand from a communal bowl may favour the spread of *H. pylori* and contribute to the high prevalence rate observed. Children in the tropics with chronic diarrhoea and associated malnutrition represent such a heterogeneous group that obtaining adequate control groups for any study is difficult. This is illustrated by the apparent association between the prevalence of high anti-*H. pylori* antibody titres and malnutrition in Farafenni children less than 30 months of age. This finding is, however, confounded by the fact that many of the malnourished children in this group also had concurrent diarrhoea. Therefore, an attempt was made in this study to control for the effects of both diarrhoea and malnutrition alone. Children with marasmus and no diarrhoea were not found to have a higher prevalence of *H. pylori* infection than healthy children of the same age, whereas in the patients with marasmus in association with chronic diarrhoea, there was a significantly increased prevalence rate of *H. pylori* infection compared with matched control groups. Chronic diarrhoea in association with marasmus

may predispose to *H. pylori* infection due to the fact that children with chronic diarrhoea and malnutrition are more unwell and more immunocompromised than children with marasmus alone. Alternatively, *H. pylori* infection itself may predispose to enteritis with other organisms by compromising the gastric acid barrier. It is also possible that both factors operate. The association between gastritis associated with *H. pylori* and hypochlorhydria is controversial.²³ Nevertheless, even a transient impairment of the gastric acid barrier at the time of infection could predispose to small bowel bacterial overgrowth and recurrent enteritis and may represent an important aspect of the pathogenesis of chronic diarrhoea and malnutrition in children in The Gambia. Further investigations of the relation between gastric *H. pylori* infection, gastric acidity, and small bowel bacterial overgrowth in children with chronic diarrhoea and malnutrition are indicated.

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Understanding non-attendance in outpatient paediatric clinics

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Abstract

Outpatient clinic appointments are often not kept. There has been little study of the reasons for this, but failure to attend may affect future health. Our study was based on the children's outpatient department of a large inner city district general hospital. The parents of 34 children who had failed to keep appointments and of 12 who did attend were interviewed in depth and the appointment systems of the hospital and of a nearby regional referral centre for children were reviewed.

At the district general hospital 23% of first appointments and 35% of subsequent appointments were not kept. We found that parents usually made a conscious decision about attending, balancing the perceived advantages and disadvantages of doing so. Their assessment of the severity of the child's illness was crucial in this. Twenty one of the 34 children who had not attended were assessed at the time of interview as still needing to attend. Of these, 16 subsequently kept an appointment and 11 underwent further investigation or treatment. We conclude that children who are not brought for outpatient appointments may be at risk of avoidable ill health and that ways of either ensuring attendance at outpatient clinics or providing alternative means of health supervision are needed.

Failure to keep outpatient appointments is common.¹⁻³ It wastes health service resources, disrupts clinic appointment systems, and may affect the patients' health. The reasons for failing to attend are not well understood. We therefore studied parents and children in a paediatric outpatient clinic to find out why parents did not bring children for appointments and whether the failure to do so might affect the children's health.

Non-compliance with medical advice has been much studied,³⁻⁷ but much less has been written about failure to keep appointments, which is a specific form of non-compliance. Previous work on non-attendance has concentrated on measuring the scale of the problem or on comparing characteristics of those who attend and those who do not.⁸ We decided to carry out in depth interviews with parents in order to understand why some do not attend. We also studied patterns of non-attendance in several outpatient clinics, including both general paediatric and subspecialty clinics, and assessed the health of children who had not been brought for appointments.

Methods

Between September 1985 and October 1986 the appointment lists and related medical records of two general paediatric clinics in a large inner city district general hospital (Dudley Road Hospital, Birmingham) were examined by one of us (RA). In 1987 a similar study was carried out in six paediatric specialty clinics at the Birmingham Children's Hospital. The purpose of these studies was to assess patterns of non-attendance in the different clinics. The service setting for the process of referral, appointment, consultation, and discharge was also assessed. This involved identifying referral routes, administrative arrangements for making appointments and procedure after failure to attend, the role of liaison health visitors, and the ways in which the clinics were organised. For this purpose interviews were held with administrative, clerical, medical, and nursing staff at the hospitals and with liaison health visitors. Eleven general practitioners were also interviewed. These results will be reported in a later paper.

The major part of the study involved in depth, semistructured interviews with one or both of the parents of a sample of 48 children who had been given appointments to attend a general paediatric clinic at Dudley Road Hospital. Interviews lasted between 35 minutes and 2 hours 5 minutes (average 1 hour 10 minutes) and all were recorded and transcribed for later analysis. All but two (who could not be traced) were seen at their home by the field worker (RA).

Children were selected prospectively from clinic appointment lists beginning in December 1986 and the sample was divided into the quotas specified in table 1. Selection continued until the last quota category was filled. While this was not a random sample we have no reason to suspect the introduction of a systematic bias. Distinction was drawn between appointments for a first consultation in an outpatient clinic (primary appointments) and those for subsequent consultations (secondary appointments).

The methods used for interviewing and for analysing interview transcripts (the 'qualitative method') were based on techniques described by Ritchie and Sykes,⁹ and RA received training in the techniques before the interview programme began. The main topics covered during the interviews were parents' perception of their child's health and symptoms, parents' account of their hospital experience, the decision about attendance, and certain characteristics of the respondents. The approach sought the respondent's own account of events and experiences

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Table 1 Selection criteria and sample quotas

	Children who did not attend		Children who attended§	
	First appointments		Subsequent appointments‡	
	A* (After admission)	B† (Referral from general practitioner)		
Dr Y	6	6	6	6
Dr Z	6	6	6	6

*Admitted as an emergency but failed to attend two primary outpatient appointments.

†Referred but on no occasion attended.

‡Four consecutive appointments given within 12 months. Attended first then failed to attend for two or more.

§Attended each consecutive appointment within a 12 month period.

Table 2 Gross non-attendance rates at eight paediatric outpatient clinics

Clinic	Appointments for first consultation (primary appointments)		Appointments for subsequent consultation (secondary appointment)	
	No given	No (%) failed to attend	No given	No (%) failed to attend
General paediatric:				
A	529	120 (23)	3131	1119 (36)
B	254	59 (23)	1025	348 (34)
C	317	87 (27)	1660	558 (34)
General surgical paediatrics	391	149 (38)	1223	267 (22)
Orthopaedic	405	131 (32)	842	415 (49)
Diabetic	15	2 (13)	1098	225 (21)
Cardiology	222	13 (6)	581	100 (17)
Oncology	32	2 (6)	2342	313 (13)

and transcripts of these accounts were later analysed. Data obtained in this way were related to our own observations of the way the clinics were organised and to information contained in the hospital records. At the time of the interview, an assessment of the child's health was made according to a profile agreed by the research team and this assessment was reviewed with a consultant paediatrician (DPA) with the hospital notes if the child had been seen in hospital.

Results

PATTERNS OF NON-ATTENDANCE

The gross non-attendance rates for the eight clinics studied are given in table 2. Attendance rates were higher in specialist clinics where many of the children might be expected to have serious or life threatening conditions. In seven of the eight clinics primary appointments were less likely to be missed than secondary. It should be noted that the gross non-attendance rates are based on appointments and not on children. Table 3 shows that the two general paediatric clinics at Dudley Road Hospital each had a gross non-attendance rate for primary appointments of about 23%, but in both clinics only about 8% of children failed to attend two consecutive primary appointments. The gross non-attendance rates for secondary appointments were 36% in clinic A and 34% in clinic B. In these clinics children were almost always removed from the appointments list after two consecutive missed appointments but from a total of 1118 missed secondary appointments, only 171 children were removed. This suggests that a substantial number of parents may be missing every second or third appointment ('playing the system').

PARENTS' DECISION NOT TO ATTEND

Table 4 summarises the main reasons for not attending, though in depth interviews revealed that the decision not to attend was usually a conscious and complex one influenced by many factors. Parents balanced the benefits of attending against the costs, and their perception of the severity of the symptoms and of their child's prognosis was crucial in this. For example, if the child's symptoms had subsided and the costs of attending were substantial (such as arranging child care for other children, taking time off work, or travel costs for very low income families) parents were less likely to

Table 3 Attendance patterns at two clinics

	Clinic A	Clinic B
Total children in cohort	444	254
No (%) who attended first appointment	359 (81)	204 (80)
No (%) who missed first, attended second appointment	50 (11)	29 (11)
No (%) who failed to attend first and second appointments	35 (8)	21 (8)
Gross non-attendance rate (%)*	(22.7)	(23.3)

*Number of failed appointments divided by number of appointments offered $\times 100$.

Table 4 Children who did not attend: principal reason for not attending

	No of cases
Child well, decided not to attend	11
Forgot appointment	10
Mother ill	3
Domestic problems or other contingencies	8
Administrative error	1
Sought private care	1
Not traced by interviewer	2
Total non-attenders	36

attend. Parents claimed that the reasons for the appointment had not always been made clear to them either by the general practitioner in the case of primary appointments or by the hospital doctor in the case of secondary appointments. Some parents disagreed with their general practitioner about the need for hospital referral.

Eleven children did not attend because their parents decided they were now well and no longer needed to attend. Of these, only two were being referred for a primary appointment by their general practitioner. The rest had already attended hospital, either as inpatients ($n=6$) or outpatients ($n=3$). It is noticeable that the diagnoses given in table 5 support the impression given by the attendance figures for speciality clinics (table 2) that attendance is likely to be better when the condition is perceived as being more serious; a not unexpected finding. Parents' experience at previous clinic visits could, of course, influence their decision about further attendance. An unsatisfactory experience at any point in the visit (reception, waiting, or consultation) could discourage future attendance and might explain why non-attendance for secondary appointments is much more common than for primary appointments.

For three children their parents' fear of the consequences of attending the clinic appeared to be an important factor. In two cases this was a fear of being told that their child had a handicapping condition and one mother's previous contact with a police officer in the casualty department had led her to fear being wrongly accused of child abuse.

Some parents had simply forgotten the

appointment. This was more likely to happen when the disappearance of symptoms was no longer a daily reminder or when the time between notification of the appointment and the date of the appointment was long (more than six months for some children). A small number of failed appointments resulted from administrative errors or from children having changed address.

HEALTH OF CHILDREN WHO DID NOT ATTEND

Thirty four of the 36 children who did not attend (table 1) were assessed at the time of the in depth interview with their parents. The results of this assessment were then reviewed with the consultant, together with their hospital records, and 21 were assessed as needing further medical attention (table 6). It is worth noting that almost half (11 of 24) of those who had previously been seen in hospital were thought to no longer need to attend. After the interview, the parents of 17 children asked for another outpatient appointment and 16 subsequently attended. Eleven of these were either given further appointments or referred to a consultant in a different specialty, in all cases for further investigation or treatment.

Discussion

It is important to recognise that much of our work is based on a small sample of parents and children using two outpatient clinics. Our conclusions are offered, not as definitive statements, but more as propositions that will require further investigation. On the other hand, we believe the study has substantially contributed to our understanding of the phenomenon and consequences of non-attendance. It provides clinicians and managers alike with a more useful framework for examining their own services.

Three major conclusions can be drawn from the study. First, our findings confirm that non-attendance is a significant problem, both numerically, and in terms of hazard to children's health. The case for finding ways to reduce non-attendance or to provide alternative means of health supervision is therefore strong.

Second, the reasons for non-attendance are not straightforward, at least in the case of children. For parents, the decision to attend or not can often be a complex one, which is importantly affected by their perception of their child's health and symptoms. They will balance the costs of attending with the perceived benefits of attending. The comments of general

Table 5 Diagnoses of children in sample. Parents' decision to attend or not attend

Children who did not attend ($n=36$)	
Diarrhoea	Febrile convulsion, idiopathic
Constipation	precocious menarche
Failure to thrive ($n=5$)	Delayed development ($n=2$)
Rectal pain and bleeding	Systolic murmur
Abdominal pain	Otitis media
Pigmentation of skin	Asthma ($n=3$)
In-toeing ($n=2$)	Chest infection
Stiff legs, odd gait	Dysuria
Febrile convulsions ($n=9$)	Bow tibia
Febrile convulsion: renal anomaly	Rickets, eczema
	Bronchiolitis, eczema
Children who attended ($n=12$)	
Apnoea, eczema oesophageal reflux	Asthma, eczema
Duplex kidney collecting system	Blind, convulsions
Haematemesis, anaemia	Microcephaly, cerebral palsy
Eczema, asthma	Microcephaly
Asthma	Epilepsy
Haemolytic uraemic syndrome	Chronic diarrhoea

Table 6 Health outcomes of the children who did not attend

	First appointments		Subsequent appointments	Total
	Referral from general practitioner	After admission		
Needed further hospital outpatient treatment	3	3	5	11
Needed further hospital diagnostic tests	5	3	0	8
Needed tests or treatment by general practitioner	0	2	0	2
No signs or symptoms of ill health	2	4	7	13
Total	10	12	12	34

practitioners and parents suggest that the case made by Marinker *et al* for improving primary referral practice could also be extended to follow up appointment practice.¹⁰ Hospital medical staff, referring general practitioners, and potentially nurses and health visitors, all have an important role in helping parents to make the most informed decision given their circumstances.¹¹

Third, the means for effective follow up of non-attenders merits further investigation. Although there are steps that could reduce non-attendance, it seems unlikely ever to be eliminated. Our evidence suggests that a substantial proportion (if not a majority) of children who do not attend can be expected to have health problems warranting further medical attention. Most of these children had already been removed from the appointment list and their general practitioner notified, but unless particular concern was expressed by a consultant, the children's general practitioner did not routinely follow them up. In the absence of our interview, the children in the study would have had no contact with health professionals until their symptoms worsened to the point where their parents would have sought medical advice. It is interesting that after the in depth interview, further outpatient appointments were requested and kept by the parents of 16 children. This suggests that follow up by a health professional (such as an appropriately trained health visitor), using a counselling approach, can be effective. Even if a child appears to have recovered, it is

important that this is confirmed (preferably by the child seeing the referring general practitioner) and that the hospital is notified to prevent further appointments being made and broken.

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Pharmacokinetics of prednisolone in children with nephrosis

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Abstract

The pharmacokinetics of prednisolone given intravenously were studied in 11 children with relapsed steroid responsive nephrotic syndrome, and four control subjects. The clearance of both total and unbound drug was decreased in these children and the unbound fraction of the drug in plasma was significantly correlated with the degree of hypoalbuminaemia. We conclude that changes in the clearance of prednisolone and altered protein binding might account for some of the variability in both therapeutic responses and the incidence of toxicity in patients treated with standard dosage regimens.

The introduction of glucocorticoid treatment of steroid responsive nephrotic syndrome reduced the mortality appreciably, but there was still considerable morbidity, with about one third of all patients having at least two relapses within six months of the initial episode. A further third continued to relapse less frequently, while the remainder had no relapses at all.¹ These differences in outcome have not been explained pathophysiologically, and there is a degree of prognostic variability despite treatment with standardised regimens of glucocorticoid drugs. Insufficient drug treatment might fail to suppress the disease adequately; on the other hand, Leisti and Koskies found a strong association between severe hypothalamic-pituitary-adrenal suppression and a high risk of early relapse.² The degree of hypothalamic-pituitary-adrenal suppression is proportional to the dose of glucocorticoid in subjects who do not have nephrotic syndrome so that an excessive dose of glucocorticoids could predispose to early relapse.³

The variable prognosis of steroid responsive nephrotic syndrome might be explained by variations in the way the body handles glucocorticoid drugs. There is considerable potential for pharmacokinetic variability both within and between patients. Glucocorticoids circulate bound to plasma albumin,⁴ transcortin,⁵ and α_1 -acid glycoprotein,⁶ and it is thought that only the unbound drug is pharmacologically active.⁴ Varying degrees of hypoproteinaemia always occur in steroid responsive nephrotic syndrome, and Lewis *et al* drew attention to the clinical importance of this by showing that there was an increased incidence of toxic effects of glucocorticoids in hypoalbuminaemic subjects.⁷ The signs of cushingoid toxic effects vary among children with steroid responsive nephrotic syndrome, some patients developing severe

complications while others are unaffected despite being given standard doses of prednisolone.

To examine the possibility that the variable prognosis of patients with steroid responsive nephrotic syndrome treated with prednisolone might be associated with changes in the pharmacokinetics of prednisolone, we have studied the kinetics of this drug given intravenously to children with acute nephrosis, using total and unbound plasma concentration times.

Patients and methods

STUDY DESIGN

Intravenous pharmacokinetic studies were performed on 11 children with relapses of steroid responsive nephrotic syndrome. Their median age was 10 years (range 4-16) and their median plasma albumin concentration was 23 g/l (range: 16-33 g/l) (table 1). Prednisolone was given as an intravenous bolus injection of prednisolone phosphate (Codelsol; Merk, Sharpe and Dohme) 30-64 mg (median: 60 mg). Ten 3 ml blood samples were taken through an indwelling intravenous cannula at 10, 15, 20, 25, 30, 60, 90, 120, 240, and 360 minutes after the injection of prednisolone. Patients were selected for the study because they were expected to be able to tolerate the experimental protocol and in addition, the patients or their parents, or both, had given consent. Ethical approval was given by Leeds Eastern District ethics committee.

Four volunteers aged 14-30 years who did not have nephrosis were also studied after having received a bolus injection of 60 mg of prednisolone. All had normal plasma albumin concentrations between 43-49 g/l (table 1).

MEASUREMENT OF PLASMA PREDNISOLONE CONCENTRATIONS

Total prednisolone concentrations were measured by high performance liquid chromatography⁸ using a 30 cm $\times$ 3.9 mm inside diameter stainless steel 10 μ m porous silica column with a mobile phase consisting of dichloromethane: ethanol:water:glacial acetic acid (500:30:30:1% v/v) at a flow rate of 2 ml/min and ultraviolet detection at 254 nm. The interassay coefficient of variation was 5.3% (n=23) at 100 ng/ml and the limit of detection was 5 ng/ml.

Unbound prednisolone concentrations were measured after ultrafiltration.⁹ A sample of plasma (1 ml) was placed in a Centrifree ultrafiltration chamber (Amicon) and centrifuged at

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Table 1 Details of children with nephrosis and control subjects

Case No	Age	Sex	Dose of prednisolone		Plasma albumin concentration (g/l)
			mg	mg/m ²	
Children with nephrosis:					
1	13	Male	65	42.5	30
2	11	Female	30	28.8	31
3	10	Male	60	61.8	18
4	16	Male	60	37.5	25
5	4	Male	45	67.2	23
6	5	Male	48	60.0	28
7	11	Male	64	44.8	20
8	8	Female	60	61.8	23
9	12	Male	64	50.0	16
10	9	Female	60	46.5	33
11	8	Male	60	65.9	16
Control subjects:					
12	30	Male	60	30.7	43
13	14	Male	60	45.5	45
14	30	Male	60	31.2	45
15	30	Male	60	32.8	49
Mean (SD)					
for children with nephrosis	9.7 (3.3)		56.0 (10.2)	51.5 (12.1)	23.9 (5.8)
Mean (SD)					
for control subjects	26.0 (6.9)		60.0 (0)	35.1 (6.0)	45.5 (2.2)

1500 g for 25 minutes at 37°C in a 35° fixed angle head. The resultant filtrate was analysed for prednisolone concentration by high performance liquid chromatography.

PHARMACOKINETIC ANALYSIS

The disappearance of both total and unbound prednisolone from plasma following intravenous injection was initially analysed using the 'C-STRIP' computer programme.¹⁰ This indicated that the decline of both total and unbound plasma prednisolone concentrations with time was biexponential. Consequently, the intravenous concentration time data was fitted to a biexponential equation ($C = Ae^{-\alpha t} + Be^{-\beta t}$) using non-linear regression analysis. This procedure gave estimates of A and B, the intercepts at time zero of the two exponential phases, and α and β , the respective slopes of each exponential phase. The kinetics of both bound and unbound prednisolone were described in terms of: (i) the half life ($t_{1/2}(\beta)$) of the terminal exponential phase of the concentration time data; (ii) the apparent volume of distribution: $V = \text{dose}/AUC \beta$ (where AUC is the area under the concentration time curve from time zero to infinity); and (iii) the plasma clearance (Cl). $Cl = \text{dose}/AUC$. The area under the concentration time curve was calculated from the equation: $AUC = A/\alpha + B/\beta$. To estimate the percentage of prednisolone unbound in plasma during the concentration time profile, an averaged value was calculated. Percentage unbound in plasma = $AUC_u \times 100/AUC_t$, where AUC_u and AUC_t are the areas under the concentration time curves for the unbound and total drug, respectively.

STATISTICAL ANALYSIS

Stepwise multiple linear regression analysis was used to discover which variables were related to each pharmacokinetic measurement and to rate these variables in order of their importance.¹¹ Pharmacokinetic measurements (area under the

concentration time curve, plasma clearance, volume of distribution, and half life (β)) were treated as dependent variables, which were regressed on dose as a function of both surface area and body weight, body weight, surface area, plasma albumin concentration, and age of the subject. Only terms that were significant in the regression equation at the 5% level were subsequently used.

Results are given as mean (SD) and the significance of differences between groups were assessed by the Mann-Whitney U test. A probability of <0.05 was accepted as significant. Clearance and apparent volume of distribution are expressed in terms of body surface area to permit comparisons to be made between children with nephrosis and control subjects.

Results

Representative profiles of total and unbound prednisolone concentration times after a 60 mg/m² intravenous dose of prednisolone are shown in fig 1. Both curves are characterised by an initial rapid distribution phase (α) followed by a slower elimination phase (β) and this pattern was repeated in all subjects studied. Analysis of these data with the 'C-STRIP' programme showed that a biexponential equation was the best fit for each subject studied. The pharmacokinetic measurements of both total and unbound prednisolone in patients with nephrosis and volunteers are shown in tables 2 and 3, respectively, and each pharmacokinetic measurement is discussed below.

AREA UNDER THE CONCENTRATION TIME CURVE AND PLASMA CLEARANCE

Tables 2 and 3 show that there was no difference between area under the concentration time curve for total concentration of the drug for patients with nephrosis and volunteers. Although the area under the concentration curve for the unbound drug was 84% greater in the group of patients with nephrosis compared

Figure 1 Disappearance from plasma of total and unbound prednisolone after intravenous administration.

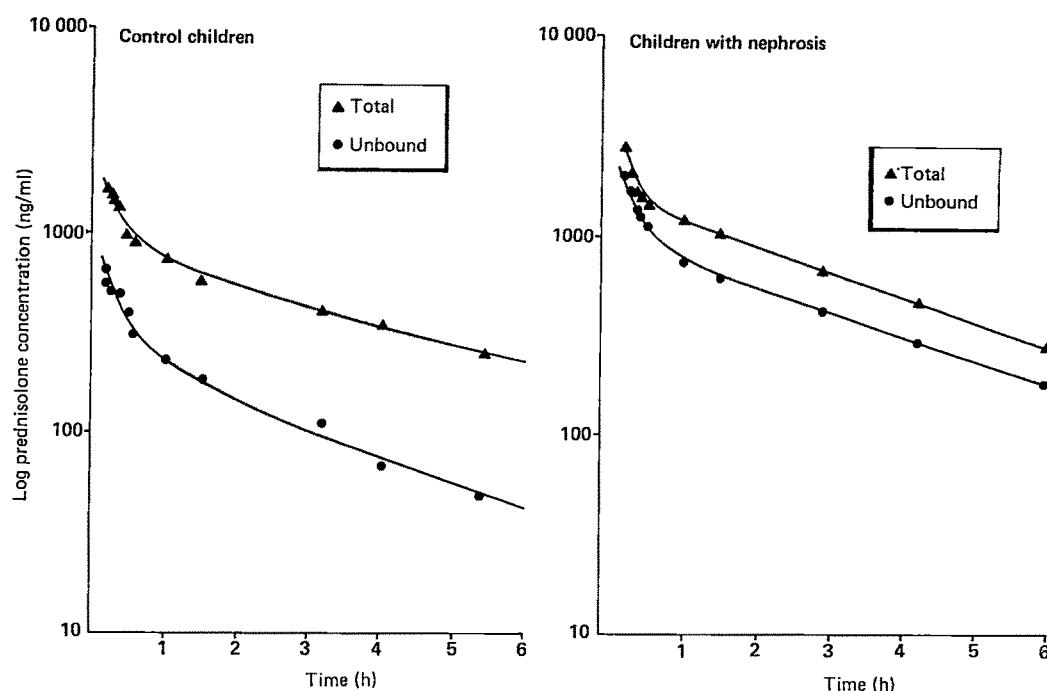


Table 2 Pharmacokinetic measurements calculated from the total and unbound concentration of prednisolone ($28.8\text{--}67.2\text{ mg/m}^2$) in children with nephrosis

Case No	Area under concentration time curve for total concentration of drug (mg/h/l)	Area under concentration time curve for unbound concentration of drug (mg/h/l)	Total plasma clearance of drug (l/h/m ²)	Plasma clearance of unbound drug (l/h/m ²)	Total volume of distribution (l/m ²)	Volume of distribution of unbound drug (l/m ²)	Half life t _{1/2} (β) (hours)
1	3.8	1.7	3.1	7.0	44.4	73.8	2.7
2	4.2	1.0	1.9	7.9	28.0	41.1	2.9
3	6.2	4.0	2.8	4.3	35.1	57.7	2.4
4	4.1	2.0	2.6	5.2	31.3	42.5	2.4
5	5.6	3.2	3.4	5.9	24.2	43.9	1.4
6	5.0	2.4	3.3	7.1	22.5	55.0	1.3
7	3.6	2.1	3.4	6.0	30.7	65.0	1.8
8	5.5	3.6	3.1	4.8	25.8	29.8	1.9
9	5.4	3.4	2.6	4.2	25.0	35.1	1.9
10	3.6	1.1	4.7	15.1	42.1	65.1	2.0
11	5.2	2.6	3.2	6.5	16.5	48.4	2.2
Mean (SD)	4.7 (0.9)	2.5* (1.0)	3.1 (0.7)	6.7** (2.9)	29.6 (8.0)	50.7* (13.8)	2.1 (0.5)

* $p > 0.01$; ** $p > 0.001$ compared with value calculated for total prednisolone.

Table 3 Pharmacokinetic measurements calculated from the total and unbound plasma concentrations of prednisolone ($30.7\text{--}45.5\text{ mg/m}^2$ given intravenously) in control subjects

Case No	Area under concentration time curve for total concentration of drug (mg/h/l)	Area under concentration time curve for unbound concentration of drug (mg/h/l)	Total plasma clearance of drug (l/h/m ²)	Plasma clearance of unbound drug (l/h/m ²)	Total volume of distribution (l/m ²)	Volume of distribution of unbound drug (l/m ²)	Half life t _{1/2} (β) (hours)
12	4.4	1.1	7.4	30.3	41.0	107.0	3.8
13	4.2	1.5	10.7	29.7	28.8	50.8	2.7
14	3.7	1.4	8.9	23.3	26.5	63.2	2.1
15	3.4	1.3	9.6	24.5	28.6	103.0	2.1
Mean (SD)	3.9 (0.5)	1.3** (0.2)	9.1† (1.4)	27.0**† (3.6)	31.2 (6.6)	81.0* (28.2)	2.7 (0.8)

* $p < 0.01$; ** $p < 0.001$ compared with value calculated for total prednisolone; † $p < 0.01$ compared with total plasma clearance and plasma clearance of unbound drug for children with nephrosis (table 2).

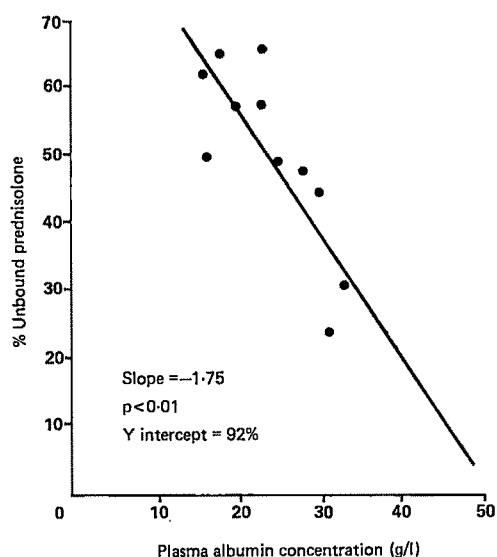
with the volunteers, this increase was not significant. Both total plasma clearance and plasma clearance of the unbound drug were, however, significantly less ($p < 0.01$) than their corresponding mean values in the volunteers (tables 2 and 3). Multiple linear regression analysis did not find any variables that correlated with total plasma clearance in patients with nephrosis, but clearance of the unbound drug was significantly

related to plasma albumin concentration ($r = 0.69$, $p < 0.05$) (fig 2).

APPARENT VOLUME OF DISTRIBUTION

Total volume of distribution was similar in the two groups when corrected for body size, but the volume of distribution of the unbound drug in the patients with nephrosis was 37% less than

Figure 2 Percentage fraction of unbound prednisolone and plasma albumin concentration in children with nephrosis.



the mean value for the volunteers (tables 2 and 3). There was, however, no significant difference between the two groups. In patients with nephrosis both total volume of distribution and volume of distribution of the unbound drug were significantly correlated with body weight ($p < 0.001$).

HALF LIFE OF PREDNISOLONE

The half life of prednisolone in both groups is shown in tables 2 and 3, respectively; there was no difference between the two study groups. The dose of prednisolone/kg body weight was the only variable to be significantly correlated with half life in patients with nephrosis ($r = 0.68$; $p < 0.05$). It is unlikely, however, that this correlation is of importance because neither total plasma clearance nor total volume of distribution were dependent on the dose of drug given.

PERCENTAGE OF UNBOUND PREDNISOLONE

In patients with nephrosis the mean of the concentration averaged value of the percent of drug unbound was 50 (13)% ($n = 11$), and in volunteers it was 30 (7.0)% ($n = 4$), though this difference was not significant.

The variation in percentage of unbound prednisolone and its correlation with plasma albumin concentration in patients with a relapse of nephrosis is shown in fig 2. As expected the relationship between these two variables was inverse ($r = -0.78$; $p < 0.01$), which suggests that as plasma albumin concentrations decrease, there is a concomitant increase in the fraction of unbound prednisolone. The intercept at zero albumin concentration, gives a value for percentage of unbound prednisolone of about 92%, which suggests that the bulk of prednisolone is bound to albumin in the range of doses tested in this study. There was no significant correlation between the percentage of unbound prednisolone and total volume of distribution, volume of distribution of unbound drug, half life, and total clearance of the drug. There was, however,

an inverse correlation between the percentage of unbound prednisolone and the clearance of unbound prednisolone ($r = -0.74$; $p < 0.001$).

Discussion

We found a mean half life of 2.1 (0.5) hours in both groups which is in agreement with other studies that have reported 1.4 to 3.5 hours.¹² The half life of prednisolone in children with nephrosis was not significantly different from that in the controls. In contrast, the clearance of both total and unbound drug was less in the children with nephrosis than in the controls. This emphasises the importance of not using half life alone to describe elimination, as this measurement is also influenced by the apparent volume of distribution. The volumes of distribution of total and unbound drug tended to be lower in patients with nephrosis, and this probably accounts for the lack of any difference in half life between the two groups. The reason for the reduced clearance of prednisolone in the patients is not clear, but it may be related to the difference in age between the patients and volunteers, or it may be that the elimination of prednisolone is impaired in children with nephrosis.

In this study we found a significant inverse correlation between the concentration averaged percentage of unbound prednisolone, and the plasma albumin concentration in children with nephrosis. A similar association between the proportion of drug in the unbound form and plasma albumin concentration has previously been shown in individual plasma samples as opposed to the complete concentration time that we used.^{13 14}

Interestingly total clearance of prednisolone was not correlated with either the plasma albumin concentration or percentage of unbound prednisolone. This suggests either that total clearance of the drug is not dependent on the fraction of unbound drug, or that the clearance of unbound prednisolone decreases as the percentage of unbound prednisolone increases. The latter explanation seems more likely, because a significant inverse relationship was found between the percentage of unbound prednisolone and the plasma clearance of the unbound drug in children with nephrosis. Total clearance would not change, because this measurement is related to the unbound fraction and clearance of the unbound drug through the relationship: total clearance equals the unbound fraction multiplied by the clearance of the unbound drug. Thus if the percentage of unbound prednisolone increased and clearance of the unbound drug decreased in proportion, no change would be expected in total clearance.

Prednisolone is largely cleared by the liver and the plasma clearance of unbound drug is a measure of the intrinsic clearance by this organ. Intrinsic clearance is dependent on the metabolic activity of the liver and as clearance of the unbound drug decreases with increasing severity of hypoalbuminaemia, it seems likely that the ability of the liver to eliminate prednisolone is impaired in children with active nephrosis. Liver function may be deranged in

nephrotic syndrome as shown by the disturbance in the regulation of plasma lipids and its apparently limited ability to synthesise plasma albumin.

What is the clinical relevance of the reduction of clearance of the unbound drug and the increase in the percentage of prednisolone that is unbound in children with nephrosis? Both these changes are likely to make more unbound active drug available to target tissues. Leisti and Koskories showed that patients who developed severe hypothalamic pituitary adrenal suppression after treatment with prednisolone are likely to relapse in the first year.² Furthermore there is a direct association between the dose of prednisolone given and the degree of hypothalamic pituitary adrenal suppression in subjects who do not have nephrosis, and so increased availability of unbound prednisolone would be expected to cause a high degree of hypothalamic pituitary adrenal suppression thereby increasing the chances of developing frequent relapses of the disease.³ Leisti and Koskories emphasised the importance of minimising prednisolone dosage to avoid causing suppression of the hypothalamic pituitary adrenal axis. The better progression of a group of children whose prednisolone was gradually tapered down compared with a more sudden cessation may be because the hypothalamic pituitary adrenal axis was allowed to recover in the former group.¹⁵ Simply reducing the duration of treatment with prednisolone is too crude an approach, as shown in a recent study.¹⁶ It is likely therefore that tailoring the dose of prednisolone to an individual patient's requirements by relating it to plasma albumin concentration and to hypothalamic pituitary adrenal suppression will be the most successful approach to reducing the number of further relapses of nephrosis.

Lewis *et al* showed that there was an increased risk of glucocorticoid toxicity in hypoalbuminaemic patients, and suggested that this was the result of increased availability of glucocorticoids through decreased protein binding.⁷ It is notable that nephrotic children receiving similar doses of prednisolone show variable degrees of toxicity, which again may be mediated through variable clearance and protein binding.

Rane and Wilson suggested that paediatric doses should be calculated using surface area because this variable correlates with several physiological factors influencing drug disposition.¹⁷ In this study the dose of prednisolone/kg body weight was more closely correlated with pharmacokinetic measurements than dose/unit surface area. Prednisolone is prescribed for children with nephrosis by some

paediatricians using body weight, and by others using surface area; we advocate the former.

In conclusion, the results of this study suggest that decreased plasma clearance of total and unbound prednisolone, together with variable protein binding, are important factors in determining the exposure of tissues to the pharmacologically active form of prednisolone in children with nephrosis. Furthermore in these patients the clearance of unbound prednisolone decreases with the severity of hypoalbuminaemia. Thus it might be advisable to reduce the dosage in accordance with albumin concentration. Additional work is required to characterise fully the disposition of prednisolone in children with active nephrosis, particularly when it is given orally and to assess the implications of the observations reported here for the clinical use of prednisolone.

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Cerebral palsy in very low birthweight infants

R W I Cooke

Abstract

Eighty one very low birthweight survivors with cerebral palsy were matched with controls by sex, gestational age, and place of birth. Using discriminant analysis, the perinatal profiles for infants with cerebral palsy and their controls were shown to differ significantly. When infants with various types of cerebral palsy were analysed with their controls the discriminating variables differed. Diplegic infants could be differentiated from controls on antenatal variables alone, but significant discrimination of hemiplegic and quadriplegic infants required the addition of postnatal variables. Cranial ultrasound appearances differed appreciably between types of cerebral palsy. Future studies should differentiate between types of cerebral palsy and include ultrasound data. Cerebral palsy in very low birthweight infants is unlikely to prove a useful outcome indicator for neonatal intensive care.

Cerebral palsy has been defined as 'a group of disorders of movement and posture due to a defect or lesion of the immature brain'.¹ It is the most prevalent severe disability in very low birthweight survivors, and has been proposed as an outcome measure for neonatal intensive care.² The assumption is that cerebral palsy is part of a continuum of causality from intra-uterine death and growth retardation, through neonatal disease, to survival more or less intact, and that perinatal care may somehow modify this. Large scale studies have shown a much higher prevalence of cerebral palsy with shorter gestation,³ but there is a lack of evidence to suggest that the perinatal profiles of very low birthweight children with cerebral palsy differ significantly from those of infants without cerebral palsy.⁴ Doubt has been cast on the value of cerebral palsy as a method of audit of neonatal intensive care, even if perinatal brain injury is responsible for the cerebral palsy. Most such studies antedate the introduction of neonatal cranial ultrasound scanning, and so no direct evidence for perinatal brain lesions was available.

Recent publications show a strong link between cerebral palsy and ultrasound scan appearances in the neonatal period,⁵ suggesting that the problem may indeed relate to perinatal events in very low birthweight infants at least. Many large aetiological studies of cerebral palsy have included all birth weights together in analyses, and also have analysed all types of cerebral palsy together as if assuming that they have the same aetiologies. Such a study design

may obscure possible associations if they apply only to one birthweight group or to only one type of cerebral palsy. Cerebral palsy is a collective diagnosis, and it has been suggested since the 19th century that the aetiology of diplegia and hemiplegia differed.⁶ More recently authors have re-emphasised the need to consider these conditions separately. This study aims to test the hypothesis that cerebral palsy in very low birthweight infants relates in the main to post-natal brain injury rather than antenatal factors, and that the aetiologies of cerebral palsy types differ.

Patients and methods

A prospective follow up of all very low birthweight infants admitted to the Mersey Regional Neonatal Intensive Care Unit has been made since January 1980 and is ongoing. All infants are frequently examined by cranial ultrasound during their hospital stay. Perinatal details, ultrasound appearances, and subsequent follow up details are stored on a database. The details of follow up and the classification of ultrasound appearances used have been published.⁵

Many different classifications of cerebral palsy have been proposed over the last century, and agreement on diagnosis between different clinicians is notoriously difficult to achieve. The great majority of infants in this study had spastic forms of cerebral palsy, although there were a small number of complex mixed and athetoid cases. The later were included in the total number of cases but not analysed separately. Spastic hemiplegia was defined as involvement of an arm and leg on the same side of the body, spastic diplegia as involvement of both legs more than the arms or involvement of the legs alone, and spastic quadriplegia (bilateral hemiplegia) as involvement of all four limbs similarly or with more severe involvement of the arms than legs. The functional abilities of the children varied greatly, but infants were only included if their impairment produced a noticeable disability. Children with a diagnosis of 'clumsiness' were not included. Much of the difficulty in classification of cerebral palsy relates to the 'evolving' presentation of the disorder as the child develops. More than half of the infants in this study have been followed up to five years or more, and all for at least two years.

All infants surviving to 2 years of age between 1980 and 1986 inclusive and with follow up diagnosis of cerebral palsy were selected. A control case was selected for each index case matched for gestational age, sex, and

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on whether the infant was a booked case, an in utero transfer, or a postnatal transfer to the unit. The reason for matching on this latter variable was that on a preliminary examination of the data, cerebral palsy was found to be twice as prevalent in survivors of in utero transfer and four times as prevalent in survivors of postnatal transfer as in those booked and born in the unit. Selection was made of the matching case with the nearest date of birth to that of the index case and, with the exception of five infants, this was within one year. Problems with matching very immature infants arose when more than one control was sought, and so the study was confined to one control per case rather than choose more controls from very different periods.

Details were abstracted from the ultrasound follow up database and the mothers' and infants' hospital records. Variables abstracted

are listed in tables 1-6 and the appendix. They were chosen to describe the social class, health, and obstetric history of the mother, and problems in pregnancy, labour, delivery, and the neonatal period. Other variables described neurological and ultrasound abnormalities in the neonatal period and the outcome at between two and five years. These variables were compared in a univariate manner between all cerebral palsy index cases and matched controls, and then between hemiplegic, diplegic, and quadriplegic infants and their respective controls. The χ^2 test, Fisher's exact test, or the Wilcoxon rank test was used as appropriate. Variables which differed significantly between index cases and controls with a probability of $p < 0.2$ were selected and used as independent variables in separate discriminant analyses with all cases of cerebral palsy, hemiplegia, diplegia,

Table 1 Univariate analysis of variables by cerebral palsy and controls, and by hemiplegia, diplegia, and quadriplegia and controls: maternal variables

Variable	All cerebral palsy (n=81)	Control	Hemiplegia (n=35)	Control	Diplegia (n=26)	Control	Quadriplegia (n=14)	Control
Mean (SD) maternal age	25.7 (5.3)	24.4 (5.4)	25.4 (5.4)	23.4 (5.0)	26.7 (4.8)	24.5 (4.9)	25.6 (6.3)	26.3 (6.9)
No (%) in social class 3 or higher	42 (52)	31 (38)	17 (49)	12 (34)	15 (58)	11 (42)	6 (43)	8 (57)
Median (range) smoking/day	0 (0-20)	0 (0-30)	0 (0-15)	0 (0-20)	5 (0-20)	0 (0-20)	10 (0-20)	10 (0-20)
No (%) primiparous	27 (33)	40 (49)	12 (34)	17 (48)	8 (40)	12 (60)	10 (71)	8 (57)
Median (range) terminations	0 (0-1)	0 (0-2)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
Median (range) miscarriages	0 (0-8)	0 (0-2)	0 (0-4)	0 (0-2)	0 (0-8)	0 (0-1)	0 (0-5)	0 (0-1)
Median (range) stillbirths	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
Median (range) neonatal deaths	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
Median (range) live children	0 (0-6)	0 (0-4)	0 (0-6)	0 (0-2)	0 (0-3)	1 (0-3)	0 (0-5)	0 (0-4)

Differences significant at $p < 0.2$ are shown.

Table 2 Univariate analysis of variables by cerebral palsy and controls, and by hemiplegia, diplegia, and quadriplegia and controls: pregnancy variables (results are number (%) unless otherwise stated)

Variable	All cerebral palsy (n=81)	Control	Hemiplegia (n=35)	Control	Diplegia (n=26)	Control	Quadriplegia (n=14)	Control
Bleeding	4 (5)	5 (6)	1 (3)	3 (9)	1 (4)	2 (8)	1 (7)	0 (0)
Hypertension	14 (17)	12 (15)	5 (14)	4 (11)	3 (12)	4 (15)	3 (21)	2 (14)
Toxaemia	12 (15)	11 (14)	5 (14)	4 (11)	2 (8)	3 (12)	2 (14)	2 (14)
Maternal illness	7 (9)	2 (3)	1 (3)	2 (6)	1 (4)	0	4 (29)	0
Amnionitis	17 (21)	6 (7)	5 (14)	3 (9)	6 (23)	1 (4)	5 (36)	2 (14)
Multiple pregnancy	20 (25)	14 (17)	8 (23)	4 (11)	8 (31)	4 (15)	3 (21)	5 (36)
Non-vertex presentation	28 (35)	27 (33)	13 (37)	13 (37)	10 (39)	7 (26)	5 (36)	5 (36)
Mean (SD) birth weight (g)	1143 (198)	1154 (223)	1168 (202)	1199 (216)	1156 (193)	1157 (205)	1037 (198)	1010 (211)
Median (range) SD score	0 (-3.5 to 2)	-0.2 (-2.8 to 2)	0.2 (-3.5 to 2)	1.2 (-3.5 to 2)	-0.45 (-3.3 to 2.6)	0 (-3 to 2)	0.5 (-2.1 to 2)	-1.2 (-2.7 to 2)

Differences significant at $p < 0.2$ are shown.

Table 3 Univariate analysis of variables by cerebral palsy and controls, and by hemiplegia, diplegia, and quadriplegia and controls: labour and delivery variables (results are number (%) unless otherwise stated)

Variable	All cerebral palsy (n=81)	Control	Hemiplegia (n=35)	Control	Diplegia (n=26)	Control	Quadriplegia (n=14)	Control
Spontaneous onset labour	70 (86)	68 (84)	4 (11)	5 (14)	4 (15)	4 (15)	1 (7)	1 (7)
Spontaneous rupture of membranes	17 (21)	23 (28)	5 (14)	7 (20)	18 (69)	18 (69)	10 (71)	7 (50)
Vaginal delivery	49 (61)	53 (65)	22 (63)	26 (74)	11 (42)	14 (54)	5 (36)	2 (14)
Contractions	70 (86)	70 (86)	31 (89)	30 (86)	22 (85)	23 (88)	14 (93)	14 (93)
Median (range) labour duration (hours)	4.5 (0-25)	6 (0-33)	6 (0-24)	6 (0-24)	4 (0-25)	6 (0-33)	4 (0-24)	6 (0-24)
Antepartum haemorrhage	17 (21)	23 (28)	5 (15)	11 (32)	7 (27)	4 (17)	5 (36)	6 (43)
Cardiotocograph abnormality	21 (26)	11 (14)	7 (29)	3 (12)	10 (40)	5 (24)	3 (27)	3 (27)
Median (range) Apgar score (at 1 min)	5 (1-10)	5 (1-9)	4 (1-10)	5 (1-10)	5 (2-9)	5 (2-9)	5 (1-9)	5 (1-9)
Median (range) Apgar score (at 5 mins)	8 (1-10)	8 (2-10)	7 (1-10)	7 (1-10)	8 (4-10)	9 (2-10)	8 (2-10)	9 (2-10)
Median (range) first pH	7.30 (6.5-7.55)	7.30 (7.01-7.54)	7.30 (6.5-7.50)	7.30 (6.6-7.50)	7.31 (7.07-7.46)	7.30 (7.0-7.50)	7.26 (7.01-7.42)	7.27 (7.0-7.45)

Differences significant at $p < 0.2$ are shown.

Table 4 Univariate analysis of variables by cerebral palsy and controls, and by hemiplegia, diplegia, and quadriplegia and controls: neonatal variables (results are number (%)) unless otherwise stated)

Variable	All cerebral palsy (n=81)	Control	Hemiplegia (n=35)	Control	Diplegia (n=26)	Control	Quadriplegia (n=14)	Control
Hyaline membrane disease	59 (73)	45 (56) p=0.02	28 (80)	20 (57) p=0.03	17 (65)	11 (42) p=0.09	10 (71)	11 (79)
Pneumothorax	19 (24)	11 (14) p=0.10	8 (23)	3 (9) p=0.18	5 (19)	4 (15) p=0.07	4 (29)	2 (14)
Median (range) ventilator days	9 (0-81)	4 (0-50) p=0.0007	9 (0-75)	3 (0-30) p=0.008	5 (0-54)	2 (0-50)	12 (3-78)	5 (0-40) p=0.02
Bronchopulmonary dysplasia	24 (29)	12 (15) p=0.02	10 (29)	6 (17)	4 (15)	2 (8)	7 (50)	3 (21)
Necrotising enterocolitis	13 (16)	4 (5) p=0.02	4 (11)	3 (9)	3 (11)	1 (4)	5 (36)	0
Septicaemia	33 (41)	19 (24) p=0.01	17 (49)	8 (23) p=0.02	7 (27)	4 (15)	4 (29)	5 (36) p=0.04
Hyperbilirubinaemia	22 (27)	15 (19) p=0.19	7 (20)	8 (23)	10 (39)	4 (15) p=0.11	4 (29)	3 (21)

Differences significant at $p < 0.2$ are shown.

Table 5 Univariate analysis of variables by cerebral palsy and controls, and by hemiplegia, diplegia, and quadriplegia and controls: neurological variables (results are number (%))

Variable	All cerebral palsy (n=81)	Control	Hemiplegia (n=35)	Control	Diplegia (n=26)	Control	Quadriplegia (n=14)	Control
Fits:								
None	42 (52)	73 (90)	18 (51)	33 (94)	19 (73)	22 (85)	2 (14)	13 (93)
1st Week	19 (24)	3 (4)	6 (17)	0	5 (19)	3 (11)	7 (50)	0
After 1st week	20 (25)	5 (6) p<0.001	11 (31)	2 (6) p<0.001	2 (8)	1 (4)	5 (36) p<0.001	1 (7)
Abnormal neurological examination at discharge	34 (42)	1 (1) p<0.001	13 (37)	0 p<0.001	5 (19)	0 p<0.05	13 (93) p<0.001	1 (7)
Ventriculoperitoneal shunt	33 (41)	3 (3) p<0.001	17 (49)	1 (3) p<0.001	4 (15)	1 (4)	10 (71) p<0.001	0

Differences significant at $p < 0.2$ are shown.

Table 6 Univariate analysis of variables by cerebral palsy and controls, and by hemiplegia, diplegia, and quadriplegia and controls: ultrasound variables (results are number (%))

Variable	All cerebral palsy (n=81)	Control	Hemiplegia (n=35)	Control	Diplegia (n=26)	Control	Quadriplegia (n=14)	Control
Early ultrasound:								
Normal	17 (21)	43 (53)	4 (11)	18 (51)	11 (42)	17 (65)	1 (7)	4 (29)
'Flare'	1 (1)	2 (2)	0	2 (6)	1 (4)	0	0	0
Subependymal haemorrhage	9 (11)	21 (26)	3 (9)	9 (26)	4 (15)	7 (27)	0	4 (29)
Intraventricular haemorrhage	23 (28)	15 (19)	6 (17)	6 (17)	7 (27)	2 (8)	7 (50)	6 (43)
Parenchymal haemorrhage	31 (38)	0 p<0.001	22 (63) p<0.001	0	3 (12) p=0.06	0	6 (43) p=0.007	0
Late ultrasound:								
Normal	21 (26)	73 (90)	5 (14)	32 (91)	14 (54)	25 (96)	0	11 (79)
'Flare'	1 (1)	0	0	3 (9)	1 (4)	0	0	0
Persistent ventricular enlargement	10 (12)	5 (6)	4 (11)	0	5 (19)	0	0	1 (7)
Periventricular leucomalacia	13 (16)	3 (4)	3 (9)	0	3 (12)	1 (4)	4 (29)	2 (14)
Porencephalic cyst	36 (44)	0 p<0.001	23 (66) p<0.001	0	3 (12) p<0.01	0	10 (72) p<0.001	0
Late parenchymal lesions:								
None	32 (40)	78 (96)	10 (29)	35 (100)	19 (73)	25 (96)	0	12 (86)
Unilateral	24 (30)	2 (3)	18 (51)	0	2 (8)	1 (4)	3 (21)	1 (7)
Bilateral	25 (31)	1 (1) p<0.001	7 (20) p<0.001	0	5 (19) p=0.04	0	11 (79) p<0.001	1 (7)

Differences significant at $p < 0.2$ are shown.

or quadriplegia and their controls as the dependent variable. The programme 'Discriminant' from SPSS-X was used.⁷ This programme uses stepwise linear regression to produce a discriminant model. Linear combinations of variables are used to distinguish between two or more categories of cases, in this instance, cases of cerebral palsy and their controls. The variables discriminate between the cases and controls and predict into which category a case or control falls based on the values of these variables. To find the linear combination of variables that best discriminates between cases and controls, stepwise methods are used to find a set of variables that maximise discriminating power as defined by various criteria. Variables are included in the analysis in order of their signifi-

cance, and the model tested for its significance in discriminating between infants with cerebral palsy and their controls. Variables are removed from the model when the addition of subsequent variables reduces the significance of their discriminant power. The level of significance of any variable required to enter the analysis was set as that associated with a value of 'F' greater than 1, and to remove a variable, 'F' less than 1. The final model is then tested by using it to assign cases to the two groups, that is, cerebral palsy and controls, and the percentage correct predictions given. The significance of the model and the residual variance (variance not explained by the model) is also shown.

For each cerebral palsy group discriminant analyses were performed for variables relating

Table 7 Discriminant analysis of variables by cerebral palsy and controls, and hemiplegia, diplegia, and quadriplegia and controls. Variables are grouped as (a) those relating to the period up until birth, (b) then including neonatal clinical variables, (c) then including neurological variables, and (d) then including ultrasound variables. Residual variance, significance, and percentage correctly predicted cases are shown for each analysis. Variables shown are those remaining in the discriminant model at the end of each stepwise analysis, and are in order of their importance in the model

Variable group	All cerebral palsy (n=81)	Hemiplegia (n=35)	Diplegia (n=26)	Quadriplegia (n=14)
(a) Maternal, pregnancy, labour, and delivery	Amnionitis, parity, maternal illness, labour, cardiotocography	Maternal age, cardiotocography, smoking	Labour, amnionitis, Apgar 5, smoking	Maternal illness, SD score
Residual variance	0.87	0.93	0.71	0.80
Predicts (%)	62	64	77	64
Significance	p=0.002	p=0.19	p=0.002	p=0.58
(b) Maternal, pregnancy, labour, delivery, and neonatal	Parity, necrotising enterocolitis, amnionitis, hyaline membrane disease, neonatal death, septicaemia, bronchopulmonary dysplasia, labour, cardiotocography, maternal illness	Septicaemia, hyaline membrane disease, maternal age, pneumothorax, SD score, cardiotocography, smoking	Labour, amnionitis, hyaline membrane disease, smoking, Apgar 5, hyperbilirubinaemia	Necrotising enterocolitis, maternal illness, ventilator days
Residual variance	0.79	0.80	0.64	0.64
Predicts (%)	66	71	81	78
Significance	p=0.0001	p=0.04	p=0.002	p=0.024
(c) Maternal, pregnancy, labour, delivery, neonatal, and neurological	Neurology, shunt, labour, parity, cardiotocography, hyperbilirubinaemia, fits, amnionitis necrotising enterocolitis	Shunt, neurology, pneumothorax, maternal age, SD score, septicaemia	Labour, neurology, Apgar 5, smoking, hyperbilirubinaemia	Neurology, shunt, necrotising enterocolitis
Residual variance	0.63	0.59	0.64	0.21
Predicts (%)	75	86	79	93
Significance	p<0.0001	p<0.0001	p=0.0007	p<0.0001
(d) Maternal, pregnancy, labour, delivery, neonatal, neurological, and ultrasound	Late ultrasound, amnionitis, labour, neonatal death, neurology, birth weight, parity	Late ultrasound, neurology, shunt, fits	Late ultrasound, labour, amnionitis, Apgar 5, smoking	Late ultrasound, shunt, necrotising enterocolitis, bilateral ultrasound
Residual variance	0.48	0.30	0.55	0.15
Predicts (%)	83	86	77	96
Significance	p<0.0001	p<0.0001	p<0.001	p<0.0001

to the period up to the time of birth, then including postnatal clinical variables, neurological variables, and finally ultrasound data. Table 7 shows the variables selected and remaining in each analysis in order of their discriminant power, the residual variance, the percentage of cases correctly predicted, and the significance of the model.

Results

During the seven year period, 1142 very low birthweight infants were admitted. Of these, 761 (67%) survived to at least 2 years of age. Eighty one of these survivors were identified on follow up as having cerebral palsy. Thirty five had a hemiplegia, 26 a diplegia, 14 bilateral hemiplegia (asymmetrical quadriplegia), one a mild symmetrical quadriplegia, and five hypotonic or athetoid cerebral palsy.

A number of clinical and ultrasound variables differed significantly between all cases of cerebral palsy and controls on univariate analysis (tables 1-6). The significant differences between cases and controls varied according to the type of cerebral palsy examined. When significant variables for all cases and controls were entered in a stepwise discriminant analyses, 83% of subjects could be correctly assigned with a residual variance of 0.48 (table 7). Most of the discriminatory power was due to ultrasound findings, in particular the late appearances. If ultrasound data was then excluded from the analysis, 75% of subjects could be correctly assigned, with most of the power due to the 'neurology at discharge' variable. If all variables not directly related to cerebral ultrasound or neurological function were excluded, only 66% could be correctly assigned, and this fell to 62% if only

variables recorded up to the time of delivery are considered.

When the discriminant analyses for the three main diagnosis groups are examined, while significant models for all diagnoses were produced, the variables selected differed considerably. The diplegic infants differed significantly from their controls on antenatal variables alone. Adding postnatal, neurological, and then ultrasound variables did not improve the discriminant power of the model, although residual variance and significance did improve. The variables selected were descriptive of a high risk mother (preterm labour, amnionitis, smoking) and of an immature infant (low 5 minute Apgar score, hyaline membrane disease, and hyperbilirubinaemia). Late ultrasound appearances were likely to be normal or minor abnormalities, and neonatal fits did not occur.

In neither hemiplegic nor quadriplegic infants was a significant model based on antenatal variables alone obtained. Adding postnatal variables to both groups produced significant models, which became more discriminant as neurology and ultrasound variables were added as well. Clinical variables selected for the hemiplegic group described an older mother with an at risk fetus (abnormality on cardiotocography and growth retardation) and an infant with serious illnesses (hyaline membrane disease, pneumothorax, ventriculoperitoneal shunt, fits, septicaemia). Severe late ultrasound changes were seen. A similar picture was seen in the quadriplegic group of a small infant with an ill mother and a chronic neonatal course (prolonged ventilation, necrotising enterocolitis, and ventriculoperitoneal shunt) and severe and often bilateral changes seen on ultrasound.

Table 6 compares the ultrasound changes

seen in each diagnosis group and matched control group during the first week of life, and later in the neonatal period.

Discussion

Although Little's hypothesis that cerebral palsy was related to perinatal events has held support for 150 years, many more recent authors have suggested that earlier developmental events, even if not causative, may increase the fetal sensitivity to perinatal insults. In the last century Freud summarised this: 'Difficult birth is merely a symptom of deeper effects that influenced the development of the fetus'.⁶ The excess of intrauterine growth retardation seen in infants at term with cerebral palsy would tend to support this concept.⁸ While two thirds of cerebral palsy occurs in term infants, the birth prevalence of cerebral palsy in the preterm infant is much higher, especially with diplegia; and appears to be rising in recent years.⁹ Freud also recognised that 'there is a specific relationship between premature birth and diplegic rigidity and difficult birth and general rigidity'. Paneth and Stark more recently suggest that 'determinants of CP [cerebral palsy] in LBW [low birthweight] infants differ from those in term infants and in particular are less closely related to birth asphyxia than they are to phenomena such as IVH [intraventricular haemorrhage]'.¹⁰ Stanley and English, however, found that 'the majority of LBW (<2000 g) CP children had perinatal profiles which are no different from LBW children without CP', and that 'IVH does not account for the majority of cases of CP in LBW infants'.⁴ Both studies antedate *in vivo* brain imaging. This study shows firstly the strong discriminant power of cerebral ultrasound examination in the neonatal period for later cerebral palsy, especially spastic hemiplegia and quadriplegia. Abnormal neurological examination at discharge and neonatal convulsions are also discriminant. This says nothing about antecedent variables, causative or contributory, but does imply that, as the abnormal ultrasound appearances are in the main not present at birth, but develop in the first few days to weeks of life, that they and the subsequently observed cerebral palsy are related to insults occurring at or after birth. The differences in ultrasound appearances noted in diplegic, hemiplegic, and quadriplegic cases of cerebral palsy suggest that the site and nature of the causative pathological lesion differs, as might be expected from their different neurological signs.

The perinatal profiles of very low birthweight infants with cerebral palsy differ significantly from controls in this study, but more obviously when different types of cerebral palsy are examined. Unlike the hemiplegic and quadriplegic infants, the diplegics could be differentiated from controls on antenatal variables alone and no improvement in the model occurred on adding postnatal variables. This would seem to show that diplegia is largely determined before birth, and relates to a high risk mother with an immature infant. On the other hand the variables that can discriminate between hemiplegic

and quadriplegic infants and their controls are operative in the immediate postnatal period, and relate to severity of neonatal diseases, their complications, and resulting ultrasound detectable cerebral lesions. The severer course of quadriplegic infants and their more extensive and frequently bilateral ultrasound lesions seem to place quadriplegics at the extreme end of the clinical range of hemiplegia.

Future epidemiological studies of cerebral palsy in very low birthweight infants should differentiate between the types of the disorder, and include data on neonatal cranial ultrasound examinations. It is unlikely that the prevalence of cerebral palsy in very low birthweight survivors will provide a useful outcome measure for neonatal intensive care.

Appendix

Variables used in the discriminant analyses

Maternal age	Years
Occupation	Registrar General's classification (I-III and IV, V and unemployed/unsupported)
Smoking	Number cigarettes smoked
Parity	Primiparous, multiparous
Terminations	Number
Miscarriages	Number
Stillbirths	Number
Neonatal deaths	Number
Live children	Number
Bleeding	Yes/no, any bleeding during pregnancy
Hypertension	Yes/no, any hypertension receiving treatment
Toxaemia	Yes/no, receiving treatment
Maternal illness	Yes/no, diabetes mellitus, renal failure, thyroid disease
Amnionitis	Yes/no, premature rupture of membranes with clinical signs of infection
Multiple pregnancy	Yes/no
Presentation	Non-vertex, yes/no
Birth weight	Grams
Standard deviation (SD) score	SD score, number of SD birth weight above or below mean for gestational age
Spontaneous onset (labour)	Yes/no
Spontaneous rupture of membranes	Yes/no
Vaginal delivery	Yes/no
Contractions	Yes/no, any uterine contractions before delivery
Labour	Duration in hours
Antepartum haemorrhage	Yes/no, whether due to placenta praevia or abruption
Cardiotocography	Yes/no, presence of significant abnormalities before or during labour
Apgar 1	Score at one minute
Apgar 5	Score at five minutes
First pH	First pH measured after birth (usually cord pH)
Hyaline membrane disease	Yes/no, diagnosis by radiography
Pneumothorax	Yes/no, during first four days
Days on ventilator	Number
Bronchopulmonary dysplasia	Yes/no, in oxygen at 28 days
Necrotising enterocolitis	Yes/no, radiography or surgical evidence
Septicaemia	Yes/no, positive blood culture in neonatal period
Hyperbilirubinaemia	Yes/no, Serum bilirubin concentration >240 µmol/l
Early ultrasound	Classified as in Cooke ⁵
Late ultrasound	Classified as in Cooke ⁵
Bilateral ultrasound	None/unilateral/bilateral, presence of parenchymal brain lesions on cranial ultrasound
Fits	None, first week, after first week of life but in newborn period
Neurology	Yes/no, abnormal neurological examination at discharge. Performed by residents, but not standardised. Mainly comments on abnormalities of tone, reflexes and visual attentiveness
Shunt	Yes/no, presence of ventriculoperitoneal shunt

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Neonatal pneumonia

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Abstract

All babies admitted to the neonatal unit during a period of 41 months were prospectively studied to find out the incidence, aetiology, and outcome of neonatal pneumonia, and the value of routine cultures of endotracheal tubes. Pneumonia of early onset (before age 48 hours) occurred in 35 babies (incidence 1.79/1000 live births). In 20 (57%) it was caused by group B streptococci. Blood cultures showed the presence of organisms in 16 of the 35 (46%).

There were 41 episodes of pneumonia of late onset in 39 babies. Thirty six of the 39 were preterm, and 34 were artificially ventilated (10% of all ventilated babies). Endotracheal tube colonisation had occurred in 94% of these, most commonly by Gram negative organisms and *Staphylococcus epidermidis*. In only one of seven cases with simultaneous bacteraemia was the same organism grown from cultures of the blood. After controlling for gestational age and duration of artificial ventilation there was no difference in the incidence or timing of endotracheal tube colonisation between babies who did and did not have pneumonia of late onset.

Ten babies with pneumonia of early onset (29%) died; all were preterm infants. Only one death (2%) was associated with an episode of pneumonia of late onset. Routine surveillance cultures were not helpful in predicting and managing pneumonia of late onset.

There are serious problems in defining neonatal pneumonia and in determining its causes.¹ This has led to a paucity of data, particularly about those infants who survive. Disease of early onset is most commonly caused by ascending infection from the maternal genital tract across the membranes,² and the baby is often septicaemic at birth.³ Pneumonia of late onset is usually caused by nosocomial infection, but occasionally by 'auto infection' from maternal organisms that colonised the infant at birth. Many of the reports about the bacteriology of neonatal pneumonia concern cultures taken at necropsy.⁴⁻⁷ The results of these studies have shown that though most babies with pneumonia do have bacteria in their lungs at the time of death, so do many babies who die without contracting pneumonia.^{4-6,7}

Routine surveillance screening by culture of aspirates from endotracheal tubes and swabs of the skin is commonplace among babies on neonatal units.⁸ Several early studies reported that this was useful both for predicting the

occurrence, and defining the aetiology, of early and late neonatal sepsis.⁹⁻¹⁴ Recent studies, however, have cast doubt on its value in neonatal septicaemia of late onset.^{8,15-17} The value of surveillance cultures in relation to pneumonia of late onset had not specifically been studied.

We have prospectively studied all babies admitted to our neonatal unit during a period of 41 months to find out the incidence, bacterial aetiology, and outcome of neonatal pneumonia. The value of routine surveillance cultures of aspirates from endotracheal tubes from babies being artificially ventilated was also studied.

Patients and methods

All babies admitted to the neonatal unit at this hospital during the 41 months from May 1984 to 30 September 1987 were studied. Pneumonia was defined as respiratory distress associated with changes on the chest radiograph that suggested pneumonia and that persisted for at least 48 hours. We therefore attempted to exclude transient episodes of atelectasis or collapse caused—for example—by misplacement of endotracheal tubes, and consolidation thought to be the result of pulmonary oedema. Recognised changes on chest radiographs included nodular or coarse patchy infiltrates, diffuse haziness or granularity on an air bronchogram, perihilar interstitial streaking, and lobar or sublobar consolidation.¹⁸ All radiographs were reviewed by one consultant paediatric radiologist who did not know the clinical findings. It was often difficult to distinguish pneumonia from hyaline membrane disease. In such cases additional evidence such as the presence of neutropenia, appearances on the chest radiograph that were not completely typical of hyaline membrane disease, or other clinical and laboratory data that supported a diagnosis of pneumonia, were sought. When doubt existed, the baby was always treated with appropriate antibiotics but was not included as a case of definite or probable pneumonia for the purposes of this study. Thus for example, a newborn baby with classical hyaline membrane disease who was subsequently shown to be colonised with group B streptococci but whose blood cultures showed no bacteria was not included as a case of probable or definite pneumonia. Cases were labelled as 'definite' pneumonia only if a respiratory pathogen was isolated from the blood. Cases were labelled as 'probable' pneumonia if blood cultures failed to show a pathogen. In these cases identification of a likely causative organism was based on the results of cultures of endotracheal tube aspirates, nasopharyngeal aspirates, and skin.

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Cases of pneumonia were divided into those of early or of late onset. Pneumonia of early onset was defined as the onset of symptoms during the first 48 hours after birth. Pneumonia of late onset was defined as the onset of illness more than 48 hours after birth.

Routine surveillance consisted of taking bacterial cultures of endotracheal tube aspirates from artificially ventilated babies three times a week. In infants in whom pneumonia was suspected, which included any newborn baby with respiratory distress, specimens were obtained by cotton wool swabs from nose, throat, eye, ear, rectum, and umbilicus; specimens of urine, blood, and cerebrospinal fluid were also collected. Collection of cerebrospinal fluid was sometimes delayed for one or more days in infants who were critically ill.

Specimens were inoculated on to blood agar plates aerobically and anaerobically, McConkey plates, chocolate agar plates in 5% carbon dioxide, and into cooked meat broth. Organisms were identified according to standard laboratory techniques.¹⁹ Sensitivities to antibiotics were determined by the method of Stokes and Ridgway.²⁰ Blood cultures were regarded as 'positive' if there was a growth of a likely pathogen within 72 hours in at least one of two bottles. Cultures of *Staphylococcus epidermidis* from blood were, however, only considered important if growth occurred rapidly (within 48 hours) in both bottles, and if the organisms showed identical antibiotic sensitivities. Probable contaminants (for example, α -haemolytic streptococci and diphtheroids) were not regarded as pathogenic.

Patterns of endotracheal tube colonisation were studied by comparing babies who had pneumonia with controls who did not, and who were matched closely for gestational age and duration of artificial ventilation. Controls were chosen by selecting the next admission to the unit who was matched to within one week for gestational age and to within two days for duration of artificial ventilation (or to within seven days for babies who were artificially ventilated for more than 28 days). The significance of differences between colonisation rates was assessed by the χ^2 test, and those in mean time to colonisation by the paired *t* test.

Results

PNEUMONIA OF EARLY ONSET

During the study period of 41 months there were 19596 liveborn deliveries in this hospital, which is a tertiary care referral centre catering for high risk pregnancies; 1960 of these deliveries (10%) were to mothers referred from outside the area. There were 35 cases of pneumonia of early onset in these babies, giving an incidence of 1.79/1000 live births. Sixteen cases (46%) of pneumonia of early onset were 'definite': that is, clinical and radiological features of pneumonia were associated with positive blood cultures. There were also 19 cases of probable pneumonia. Of the 16 definite cases, 11 (69%) were caused by group B streptococci, although *Streptococcus pneumoniae* infection occurred in three and untypable

Table 1 Potential risk factors for sepsis in 35 babies with pneumonia of early onset

	Total No	No with only one risk factor
Spontaneous onset of preterm labour	23	17
Prolonged rupture of membranes (>18 hours)	9	2
Maternal fever (>37.5°C)	3	1
Smelly liquor	2	0
No risk factors	8	—

Haemophilus influenzae in two babies. Five babies with pneumonia caused by group B streptococci, two in whom it was caused by *S pneumoniae*, and one in whom it was caused by *H influenzae* died, giving a mortality of 50% for definite pneumonia. None of these babies had meningitis. Of the 16 babies with definite pneumonia, 15 had a full set of cultures obtained from sites on the skin, and nasopharyngeal and endotracheal tube aspirates. Nasopharyngeal aspirates were positive for the organism obtained from blood cultures in 12 of 15 cases (80% sensitivity for predicting septicaemia). If all sites were included this rose to 13 cases (87% sensitivity).

Among the cases of probable pneumonia, cultures of endotracheal or nasopharyngeal secretions, or superficial sites, or both, grew a potential pathogen in 10 of 19 cases (53%). Group B streptococcus was the organism isolated in nine cases, group F streptococcus in one, and no organism in nine cases. Two babies with probable group B streptococcal pneumonia died. The overall mortality from pneumonia of early onset (both definite and probable) was 10 of 35 (29%). The signs and symptoms of those babies who died was similar whether the disease was caused by group B streptococci, *S pneumoniae*, or *H influenzae*. Deterioration was generally rapid, and both the course and the radiological appearances closely mimicked those of severe hyaline membrane disease. Twenty three cases of pneumonia of early onset (66%) occurred in preterm infants of less than 37 weeks' gestational age at birth, and 10 (43%) died. None of the 12 who had been born at term died.

Potential risk factors are shown in table 1. In eight cases (23%) there were no clear risk factors for the early development of sepsis. In 20 cases (57%) there was only one risk factor, and in seven cases (20%) there were two or more risk factors. Where a single risk factor was identified, this was usually the spontaneous onset of preterm labour (85%). It was noteworthy that in those babies for whom spontaneous onset of preterm labour was the only risk factor, the diagnosis by the admitting junior doctor was almost invariably that of hyaline membrane disease alone. Sepsis had, however, been included in the initial differential diagnosis for all babies with other risk factors for infection such as prolonged rupture of membranes or smelly liquor.

PNEUMONIA OF LATE ONSET

Forty one episodes of pneumonia of late onset

occurred, in 39 babies (tables 2 and 3). Thirty six of these babies (92%) were preterm. Four had already had episodes of pneumonia of early onset. Thirty four (87%) were being artificially ventilated at the time they developed pneumonia. The indication for artificial ventilation was hyaline membrane disease in all except one baby, who had been born at term and had meconium aspiration syndrome. The mean gestational age of these babies was 28 weeks and the mean time to onset of pneumonia was 35 days. Two thirds had been artificially ventilated for more than 21 days. Pneumonia of late onset developed in 36 of 358 (10%) babies who were artificially ventilated for more than 24 hours. Only one baby died of pneumonia in this group—a baby with cystic fibrosis who has previously been described.²¹ Several babies died later, however, of extreme prematurity.

Seven episodes (17%) of pneumonia of late onset were definite, with positive blood cultures (table 2). In all cases the organisms grew rapidly within 48 hours in both bottles. Two of the babies (one of whom died) each grew two organisms from blood cultures, and these were not thought to be contaminants. In one instance was the same organism grown from the blood cultures and from the endotracheal or naso-

pharyngeal secretions. In three of the other six cases antibiotic treatment for suspected pneumonia based solely on cultures of endotracheal aspirates would have resulted in inappropriate antibiotics being given.

The organisms isolated from endotracheal tube cultures in 34 babies with probable pneumonia of late onset are shown in table 3. It can be seen that Gram negative bacilli predominate, although *Staphylococcus aureus* was also found fairly often. Multiple isolates were common.

Endotracheal tube colonisation was present in 34 of the 36 intubated babies who developed pneumonia of late onset (94%) compared with only 80 of 194 babies ventilated during the study period (41%) ($p < 0.001$, table 4). After controlling for duration of artificial ventilation and gestational age, however, it was found that there was no significant difference between the rate of colonisation in the two groups (only 30 of the babies could be appropriately matched). Furthermore, there was no difference in the average time to colonisation between babies who did and did not have pneumonia, nor was there any difference between the different organisms that were cultured from the endotracheal tube aspirates in the two groups.

All cases of pneumonia of late onset were initially treated with flucloxacillin and either netilmicin or gentamicin given intravenously. An increase in ventilatory support was usually necessary. In seven of 41 episodes (17%) one or more of the organisms from the endotracheal tube was resistant to the particular antibiotics being used. Most babies recovered rapidly and it was rarely necessary to change the antibiotics.

Discussion

The diagnosis of neonatal pneumonia is difficult and though there is much information from necropsy reports there is little from clinical and laboratory studies of surviving babies. One area of difficulty is the close similarity between hyaline membrane disease and neonatal pneumonia, with or without hyaline membrane disease. Our case definition of pneumonia is fairly rigorous, and the incidence of neonatal pneumonia has probably been underestimated. We have not been able to show clearly the aetiological agent in those babies who we thought had pneumonia but who had negative blood cultures. In pneumonia of early onset when babies are heavily colonised with pathogenic bacteria such as group B streptococci, it seems likely that in most cases this is the relevant pathogen. In nine early cases and four late

Table 2 Bacterial isolates from seven babies with pneumonia of late onset (presenting after 48 hours of age)

Case No	From blood culture	From culture from nasopharynx or endotracheal tube
1	<i>Pseudomonas aeruginosa</i> , <i>Achromobacter xylosoxidans</i>	No growth
2*	<i>P. aeruginosa</i> , <i>Streptococcus faecalis</i>	No growth
3	<i>S. epidermidis</i>	<i>S. aureus</i>
4	<i>S. epidermidis</i>	Coliform sp <i>S. faecalis</i>
5	<i>P. aeruginosa</i>	<i>P. aeruginosa</i>
6	<i>S. epidermidis</i>	<i>P. aeruginosa</i>
7	<i>S. epidermidis</i>	Coliform sp Coliform sp

*Baby subsequently diagnosed as having cystic fibrosis and died.

Table 3 Bacterial isolates from nasopharyngeal or endotracheal secretions of 32 babies during 34 probable episodes of pneumonia of late onset

Gram negative bacilli:	30
Coliform sp	15
<i>P. aeruginosa</i>	12
<i>Escherichia coli</i>	2
<i>Proteus mirabilis</i>	1
<i>S. aureus</i>	5
<i>S. epidermidis</i>	2
Group B streptococcus	1
<i>H. influenzae</i>	1
No organism identified	4

Table 4 Colonisation of endotracheal tubes in babies who were artificially ventilated for longer than 24 hours, and presence of pneumonia of late onset

	No who had pneumonia	No (%) colonised	No who did not have pneumonia	No (%) colonised	p Value
Before controlling for gestational age and duration of ventilation	36	34 (94)	194	80 (41)	<0.001
After controlling for gestational age and duration of ventilation*	30	28 (93)	30	25 (83)	0.4

*Mean (range) times to colonisation in those with and without pneumonia were 8 (1–15) and 10 (2–39) days, respectively ($p > 0.05$).

cases, however, no organism was cultured either from blood or surface cultures.

In this study we have not specifically investigated the role of other pathogens, which are now attracting increasing interest from various investigators. These organisms include *Ureaplasma urealyticum*, *Mycoplasma* sp, *Chlamydia trachomatis*, *Pneumocystis carinii*, and viruses.²²⁻²⁴ It is possible that some of these organisms were responsible for infection in cases of pneumonia in which the blood culture was negative.

In early disease, the group B streptococcus remains the most important pathogen in our unit. As there is much local variation in the range of organisms causing sepsis it is important that each neonatal unit monitors its own predominant organisms. An increase in the proportion, for example, of *H influenzae* infections may suggest the initial antibiotic policy should be reviewed.

Although the overall mortality for pneumonia of early onset remains high, it is encouraging to note that in the study period no deaths occurred in babies born at term who had pneumonia of early onset. This must partly reflect the increased awareness of sepsis by midwifery and junior medical staff in our maternity and neonatal units. It is important to recognise, however, that risk factors are often absent in babies who develop pneumonia of early onset, and that spontaneous onset of preterm labour is in itself an important risk factor. Our findings support the practice of many units that all pre-term babies with respiratory distress should be given antibiotics intravenously for at least 48 to 72 hours until the results of blood cultures are available.

We have shown that endotracheal tube colonisation occurs equally in babies whether or not they have pneumonia of late onset. There seems to be a poor correlation between blood cultures and cultures of endotracheal and nasopharyngeal aspirates in these babies. This casts doubt on whether the organisms cultured from the nasopharynx or endotracheal tube are truly those causing the pneumonia. Clearly babies should not be treated for 'pneumonia' because of endotracheal colonisation with a potential pathogen if there are no accompanying radiological changes. Furthermore, reliance on the results of cultures from endotracheal tube aspirates and the accuracy of their antibiotic sensitivities will often lead to inappropriate antibiotic treatment.

Although there are some published data to support the practice of taking endotracheal cultures from babies with suspected sepsis at birth,¹²⁻¹⁴ there is conflicting evidence about the role of routine surveillance in predicting and managing neonatal sepsis of late onset.^{8-11 15-17} The practice of routine surveillance of endotracheal tube aspirates is widespread.⁸ We have previously shown that routine surveillance cultures are an inefficient means of predicting the aetiology of late septicaemia, and that considerable caution should be exercised in making decisions about antibiotic treatment based on colonisation patterns in neonatal units.¹⁶ Two other studies have recently been published

supporting this view. Evans *et al* analysed their experience of surveillance cultures from over 3000 infants,⁸ and showed that the sensitivity, specificity, and positive predictive value of such cultures are generally poor and of limited value in predicting the aetiology of neonatal sepsis, as well as being expensive. Slagle *et al* from New York have investigated the role of routine endotracheal tube cultures in the prediction of late sepsis (though not specifically pneumonia) in artificially ventilated babies.¹⁷ In their study, an organism was isolated from both the blood culture and the endotracheal tube aspirate culture in only five of 26 cases of proved sepsis (19%), though in a further seven cases the organism in the blood was also found as one of multiple isolates in the endotracheal tube culture. They also showed that inappropriate antibiotic treatment would have been given in a large number of cases (42%) if the antibiotic choice had been based on the sensitivity of the predominant isolates from the endotracheal culture.¹⁷ Our data also suggest that routine surveillance cultures contribute little to the prediction and management of pneumonia of late onset, and may even be misleading. A baby with pneumonia should be treated according to the unit's antibiotic policy rather than its own surveillance cultures. There may, however, be some role for more limited surveillance of the organisms colonising the highest risk babies in the neonatal unit, because their resistance patterns may help to formulate antibiotic policies.²⁵

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Prognosis of Down's syndrome with acute leukaemia

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Abstract

The outcome in children with acute leukaemia with ($n=90$) and without Down's syndrome ($n=4377$) was compared. Sixty three (70%) of those with Down's syndrome had acute lymphoblastic leukaemia and in comparison with 3664 (84%) controls had similar prognostic features except for a significant excess of the 'common' immunological subtype of acute lymphoblastic leukaemia. The outcome of the children with Down's syndrome was significantly worse with a five year overall actuarial survival of 28% compared with 59% in the control group. It appeared that both suboptimal chemotherapy and a high rate of infective problems contributed to the poor survival. Twenty six children with Down's syndrome had acute myeloblastic leukaemia and were significantly younger and had a higher percentage of the megakaryocytic and erythroid subtypes of acute myeloblastic leukaemia than the 713 controls. The outcome was similar in the two groups.

It is concluded that the patients with Down's syndrome who develop acute leukaemia should receive standard protocols without modification, but aggressive supportive care is necessary to improve outcome.

The first reported case of the occurrence of Down's syndrome and acute leukaemia was made in an infant in 1930.¹ It was over 30 years later before Krivit and Good, in a nationwide American survey, found more than a casual association between these two conditions.² Further studies showed that children with Down's syndrome had a 15-30 fold increased incidence of leukaemia.^{3,4} The life expectancy of children with Down's syndrome has increased with more effective treatment of respiratory infections and congenital heart disease. In a recent cohort from Canada 81.9% who had no major congenital heart disease were still alive at 20 years, though substantially fewer of those with congenital heart disease survived.⁵ There has thus been an increase in the proportion of children with Down's syndrome surviving to develop leukaemia. This factor coupled with the concept that these children should be treated as normal children and be given every opportunity of cure for any life threatening disease has increased the numbers being referred to specialist paediatric oncology and haematology centres.

With this in mind the aim of the study was to investigate the present outcome of children with Down's syndrome and acute leukaemia.

Patients and methods

The National Registry of Childhood Tumours at the Childhood Cancer Research Group (CCRG), with ascertainment based on the national cancer registration scheme, includes the great majority of children aged under 15 years with malignant disease in Great Britain.⁶ The United Kingdom Children's Cancer Study Group (UKCCSG) has a register of patients treated by its members throughout the United Kingdom and the Irish Republic and a copy of this register is also kept at the CCRG. The files of both registers were searched for children with Down's syndrome and acute leukaemia diagnosed between 1971 and 1986, and those patients treated by members of the UKCCSG at 17 centres were identified. Permission was requested to use these patients in the study. Questionnaires were completed either by one of the authors (GAL, 40%) or by members of the UKCCSG. Information gathered included congenital abnormalities, clinical features, pretreatment investigations (including chromosome analysis), treatment, and outcome. Follow up continued until October 1988.

Ninety eight children were identified with Down's syndrome and acute leukaemia. Eight patients were excluded from the study: one child was more than 15 years of age at diagnosis and the remainder were incorrectly diagnosed or had insufficient information available. Ninety children were thus included in the study, of whom 63 (70%) had acute lymphoblastic leukaemia, 26 (29%) had acute myeloblastic leukaemia, and one patient had unspecified leukaemia. This distribution is similar to the incidence reported by Rosner and Lee in 1972.⁷ This represents 68% of the patients on the National Registry with Down's syndrome and acute leukaemia diagnosed and treated in mainland Britain. The 90 children with Down's syndrome in the study were compared with 4377 children without Down's syndrome with acute leukaemia who were ascertained from the National Registry, and treated by UKCCSG members, who were diagnosed between 1971 and 1986.

Patient characteristics and survival of the two groups were analysed using standard statistical methods. Survival rates were also compared for children with Down's syndrome receiving different intensity treatment. Differences between survival curves were analysed using log rank tests.⁸

Results

CLINICAL FEATURES

The presenting features of the 63 children with

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and 3664 children without Down's syndrome who had acute lymphoblastic leukaemia are shown in table 1. There was no difference between the groups in sex, age, or presenting white cell count. There was a significantly higher proportion of the common immunological phenotype of acute lymphoblastic leukaemia in the group with Down's syndrome ($\chi^2=4.03$ on 1 df, $p<0.05$), and a corresponding deficit of T cell acute lymphoblastic leukaemia.

Children with Down's syndrome were classified by mode of treatment. Group O (five patients) received no treatment because either the patient died before treatment started (one patient) or a positive decision was made not to treat (four patients); two of these children had ventricular septal defects with pulmonary hypertension.

Group I (19 patients) received one or two drug induction, and 64% of the patients available for central nervous system directed treatment received it.

Table 1 Acute lymphoblastic leukaemia: patient characteristics. Results are number (%)

	With Down's syndrome	Without Down's syndrome
Sex:		
Male	35 (57)	2095 (57)
Female	26 (43)	1569 (43)
Total	61	3664
Age (years):		
0-1	6 (10)	406 (11)
2	7 (11)	558 (15)
3	11 (17)	584 (16)
4-6	16 (25)	988 (27)
7-9	14 (22)	539 (15)
10-14	9 (14)	589 (16)
Total	63	3664
Presenting white cell count ($\times 10^9/l$):		
<20	40 (65)	2310 (64)
20-99	18 (29)	859 (24)
≥ 100	4 (6)	452 (12)
Total	62	3621
Phenotype:		
Common	31 (91)	1251 (75)
Null cell	2 (6)	127 (8)
T cell	1 (3)	264 (16)
B cell	0	35 (2)
Total	34	1677

Table 2 Prognostic factors for patients with Down's syndrome and acute lymphoblastic leukaemia in treatment groups I and II.* Results are number (%)

	Group I	Group II
Sex:		
Male	13 (68)	19 (51)
Female	6 (32)	18 (49)
Total	19	
Age (years):		
<2	2 (10)	3 (8)
2-9	14 (74)	33 (84)
≥ 10	3 (16)	3 (8)
Total	19	39
Presenting white cell count ($\times 10^9/l$):		
<20	14 (74)	24 (63)
20-99	4 (21)	11 (29)
≥ 100	1 (5)	3 (8)
Total	19	38
Immunological phenotype:		
Common	7 (100)	23 (88)
Null cell	0	2 (8)
T cell	0	1 (4)
Total	7	26

*Group I: minimal treatment; group II: three or more drug induction.

Group II (39 patients) received (more intensive treatment and 34 (87%) received central nervous system directed treatment. Only nine of these patients were not included in United Kingdom acute lymphoblastic leukaemia (UKALL) trials, eight (21%) were treated on the UKALL X protocol, although many patients did not adhere strictly to the protocol.

Prognostic factors in the treatment groups were compared and there was no significant difference (table 2).

The presenting features of 26 children with Down's syndrome and acute myeloblastic leukaemia were similarly compared with 713 children with acute myeloblastic leukaemia but without Down's syndrome (table 3). There is a highly significant difference in age distribution with more children with Down's syndrome under 2 years of age ($\chi^2=23.97$ on 2df). This difference may in part be accounted for by the high number of erythroleukaemias (M6) observed in the group with Down's syndrome. Erythroleukaemia is predominantly a disease of children under 2 years. Both megakaryocytic leukaemia (M7) and erythroleukaemia (M6) were relatively more common. Erythroleukaemia was significantly more common when compared with all other French-American-British classification (FAB) subtypes ($p=0.004$, Fisher's exact test).

Eight of the patients with acute myeloblastic leukaemia (31%) were not treated, seven (27%) received only minimal treatment with less than three drugs (group I), 11 patients (42%) underwent intensive chemotherapy, albeit with treatment adjustments (group II).

Successful chromosome analysis from the leukaemic clones was performed in 12 acute lymphoblastic leukaemia cases and 14 cases of acute myeloblastic leukaemia. The abnormal karyotypes are shown in table 4. With this limited data no conclusions can be drawn in relation to outcome.

OUTCOME

Acute lymphoblastic leukaemia

The 58 children with acute lymphoblastic

Table 3 Acute myeloblastic leukaemia: patient characteristics. Results are number (%)

	With Down's syndrome	Without Down's syndrome
Sex:		
Male	15 (58)	374 (52)
Female	11 (42)	339 (48)
Total	26	713
Age (years):		
<2	16 (62)	152 (21)
2-9	8 (31)	334 (47)
≥ 10	2 (7)	227 (32)
Total	26	713
Presenting white cell count ($\times 10^9/l$):		
<20	19 (73)	378 (55)
20-99	7 (27)	198 (29)
≥ 100	0	110 (16)
Total	26	686
FAB subtype*:		
M1-5	7 (44)	475 (91)
M6	5 (31)	29 (6)
M7	4 (25)	17 (3)
Total	16	521

*FAB: French-American-British classification.

Table 4 Karyotype of abnormal leukaemic clone (n=8)

Type of acute leukaemia	Karyotype	Outcome
Acute lymphoblastic	47XY,+21,del(16)(P11)	Died (infection)
Acute lymphoblastic (common)	47XX,+21,1q ⁺	Died (infection)
Acute myeloblastic	47XX,+21,6q ⁻	Alive event free
Acute myeloblastic	48XY,+8,+21	Died (no treatment)
Acute myeloblastic (M4)	47XY,+21,1p ⁺ ,der(7)	Died (infection)
Acute myeloblastic (M6)	47XX,+21,t(16+18)(q22;q23)	Died (relapse)
Acute myeloblastic (M6)	51XY,+11,+13,+19,+21,+21	Died (relapse)
Acute myeloblastic (M7)	47XY,+21,del(7p13-ptder)	Died (relapse)

leukaemia and Down's syndrome who were treated had a significantly worse overall actuarial survival than those without Down's syndrome who were treated ($\chi^2=36.2$ on 1 df, $p<0.001$) (fig 1). The five year survival for those with Down's syndrome was 28% (95% confidence interval 14.2 to 42.6) compared with 59% (95% confidence interval 56.6 to 60.6) for those without Down's syndrome.

For the children with acute lymphoblastic leukaemia and Down's syndrome survival rates in the two treatment groups were compared. Relapses and causes of death are summarised in table 5. In the minimally treated group I (19 patients) there were no event free survivors. Only one child has survived and is still receiving chemotherapy after a central nervous system relapse while on treatment. In group II, 11 of the 39 patients (28%) are event free survivors with a follow up time of two to nine years from diagnosis and a median event free survival of 18 months (fig 2). There was a significant difference in the relapse free survival between the two groups ($p<0.01$). In group II six children had central nervous system relapses and two are long term survivors 13 years and eight years from diagnosis, although the latter child is still on continuous treatment four years from relapse. A third child remains on treatment because of recent bone marrow and central nervous system relapse. Two patients had a central nervous system relapse in group I, one patient from group I and one from group II

received no central nervous system directed treatment.

A substantial proportion of patients died from infection: four patients (21%) in group I and 11 children (28%) from group II. Four of the group II patients died during induction and one during an intensification module. The remaining infections occurred in remission during continuing treatment. In addition one child in group II died of infection but was found to have relapsed at postmortem examination. Deaths occurred at a wide range of ages between 17 months and 14 years. There was a variety of causative organisms. Six patients died due to unidentified pathogens causing septicaemia or pneumonia. In group I, two patients died of bacterial septicaemia: one from viral hepatitis and the other from varicella pneumonitis. In group II, most died due to presumed bacterial infections but one patient died from mycoplasma pneumonia, one from *Pneumocystis carinii* pneumonia, and a further patient died from a combination of measles and *P carinii* pneumonia (table 6). Two children died as a consequence of their congenital heart disease associated with pneumonia while on continuous treatment.

The analysis of deaths from infection showed no significant difference between the two treatment groups. The five year mortality rate conditional on not having died of their leukaemia was 47% in group I and 37% in group II. The deaths in group II tended to occur earlier; the mortality rate during the first year from diagnosis was 28% in group II compared with only 5% in group I.

Acute myeloblastic leukaemia

The five year overall survival rate was 19% (95% confidence interval 15.3 to 23.3) for those without Down's syndrome and 14% for those with Down's syndrome and acute myeloblastic leukaemia (the confidence interval could not be calculated because there were insufficient survivors).

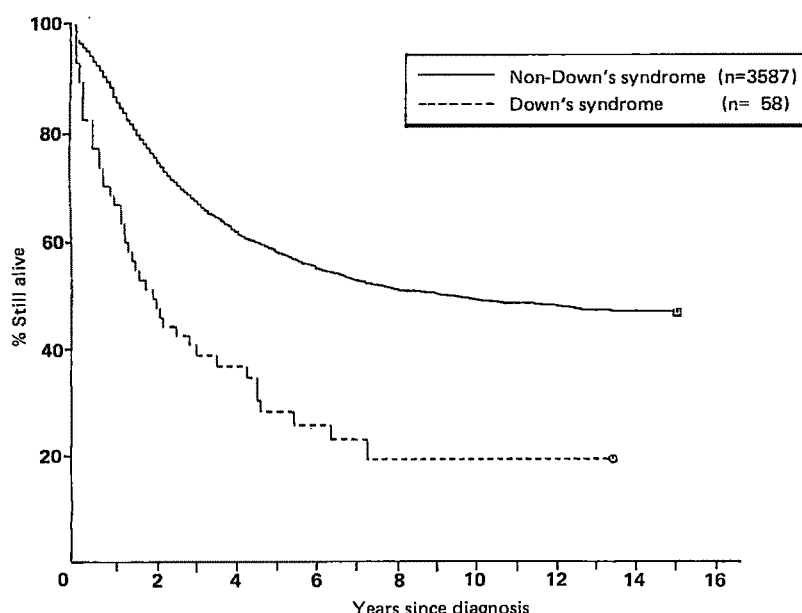


Figure 1 Survival of patients with acute lymphoblastic leukaemia with or without Down's syndrome 1971-86.

Table 5 Outcome with Down's syndrome and acute lymphoblastic leukaemia in treatment groups I and II*

	Group I	Group II	Total
No of children	19	39	58
Event free survivors	0	11	11
Induction failure	4	1	5
Relapse	9	16	25
Infective deaths	4	12†	16
Death associated with congenital heart disease	0	2	2
Status epilepticus	1	0	1

*Group I: minimal treatment; group II: three or more drug induction.

†One child died of infection but postmortem examination showed bone marrow relapse.

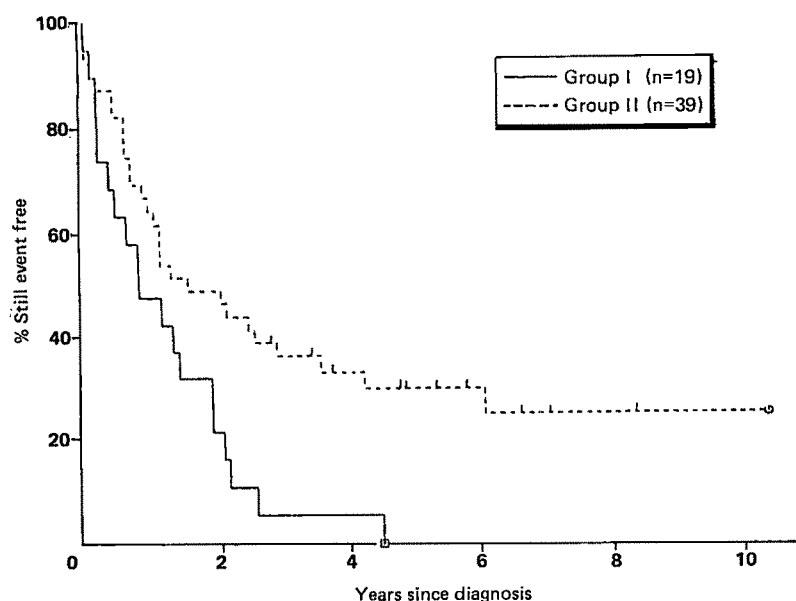


Figure 2 Percentage of patients with Down's syndrome and acute lymphoblastic leukaemia still event free. Vertical bars represent patients with less than 10 years of continuous remission.

Table 6 Causes of death from infection in patients with Down's syndrome

	Group I	Group II	Total
Total No of infective deaths:	4	12	16
Respiratory infection	1	4	5
Septicaemia	2	6	8
Organisms isolated:			
Varicella	1	0	1
Hepatitis	1	0	1
Measles	0	1*	1
Mycoplasma	0	1	1
Candida	0	2	2
Bacteria	2	3†	5
Deaths associated with congenital heart disease	0	2	2

*Plus *Pneumocystis carinii*.

†One patient had candida in addition.

There were no survivors among the seven children in group I; at best, only partial remission was obtained and the last child died of relapse while on treatment. Three children have survived in group II with an event free survival of 27% with follow up of 33 months to six years. One child was a non-responder with chronic heart failure; two children relapsed on treatment and one off treatment. There were five treatment related deaths. Two children died of infection during induction and one child of fungal pneumonia on continuous treatment. Two children, both off treatment, died due to cardiomyopathy presumably due to daunorubicin; one child had been retreated for a bone marrow relapse. One patient had a known atrial septal defect but the other had a normal echocardiogram at diagnosis.

Discussion

The children with Down's syndrome in this series have very poor survival rates. Those with acute lymphoblastic leukaemia had a very much lower overall survival rate (28% at five years) than those without (59%). The poor survival occurred despite the prognostic factors, age,

and presenting white cell count being similar, and a higher proportion of the children with Down's syndrome and acute lymphoblastic leukaemia had the common acute lymphoblastic leukaemia immunological phenotype. The similarity in the responsiveness of disease is also borne out by the fact that 97% of children in group II achieved remission, excluding two children who died of infection before remission could be confirmed. This result is very similar to that found in the study of Miller *et al* using vincristine, prednisolone, and crisantaspase (asparaginase) as induction drugs.⁹

This study does highlight a number of reasons for the survival difference. The treatment regimens used are obviously very important. In the minimal treatment group, only 79% achieved remission and there were no event free survivors. Tolerance of the continuous treatment was poor in children with Down's syndrome and many reports were received commenting on decreased compliance owing to mucositis, myelosuppression, and infection. There is evidence that within the UKALL trials strict compliance with the protocols substantially reduced the relapse rate.¹⁰ Peeters and Poon studied 24 patients with Down's syndrome and acute lymphoblastic leukaemia and found intolerance to methotrexate, with patients reaching only 30–50% of the standard methotrexate dose (methotrexate 20 mg/m² orally once weekly).¹¹ This feature was also noted by Blatt *et al*, who suggested that there may be abnormal metabolism of methotrexate causing raised serum concentrations.¹²

Primary disease of the central nervous system was not a feature in the children with Down's syndrome but eight children had a central nervous system relapse, two associated with bone marrow relapse. Of the eight children, two had received no treatment directed at the central nervous system. No child developed overt complications from either radiotherapy or intrathecal chemotherapy, although prospective psychological testing was not included in this study. The numbers of children are too small to draw any conclusion as to whether central nervous system directed treatment contributed to the infective deaths. One child died in status epilepticus but had received no central nervous system treatment and another child had epilepsy before diagnosis and received only intrathecal methotrexate. These findings strongly suggest that children with Down's syndrome and acute lymphoblastic leukaemia should receive the same central nervous system directed treatment as those without Down's syndrome.

Robison *et al*, in their 10 year survey comparing children with acute lymphoblastic leukaemia and without Down's syndrome, found the five year overall survival lower in the group with Down's syndrome (50% compared with 65%).¹³ Induction failure was higher in the children with Down's syndrome (19% compared with 6%), but the relapse free survival was not significantly different.

One of the main causes of mortality in children with Down's syndrome but without leukaemia is infection, so the fact that many

of these children with acute lymphoblastic leukaemia succumb to overwhelming infection is not surprising, although it is a worrying feature in their treatment. Induction deaths owing to infection occurred in 5% of group I and 13% in group II. The high incidence continued during maintenance with a further eight children dying in group II. These figures contrast with the incidence of 0.5% in an analysis of 184 children at the Hospital for Sick Children, London, undergoing induction treatment for acute lymphoblastic leukaemia.¹⁴ A further study from the same centre in 1981 showed 8% of children died from infection while on continuous treatment.¹⁵ Most deaths occurred in children under 5 years and as many as 16% were thought to be due to measles. In the group with Down's syndrome, 24% died of infection, but no particular pathogen was responsible. Advancing age did not appear to be a protection against infection in these children, who had a mean age of death of 6 years, with 63% over 5 years of age at the time of death. Five children died of pneumonia, a common problem in children with Down's syndrome, and in two of these congenital heart disease contributed to cause of death. The immune system has been extensively studied in patients with Down's syndrome with conflicting results, but abnormalities of the thymus,¹⁶ T cell and subsets activity,¹⁶⁻¹⁹ and neutrophil function¹⁶ have been well documented. Impaired immune surveillance may in part account for the increased incidence of haematological malignancies seen with these children.

The children with Down's syndrome and acute myeloid leukaemia presented at a younger age than controls; this has been reported before¹³ and there was a higher percentage of megakaryocytic leukaemia¹⁷ and erythroleukaemia. As reported in the paper of Robison *et al* there was no significant difference in survival from children without Down's syndrome.¹³ The use of doxorubicin or other cardiotoxic drugs must be monitored with care even in children without congenital heart disease—as shown by our two patients who suffered irreversible cardiomyopathy, one of whom had a normal echocardiogram.

We conclude that patients with Down's syndrome and acute leukaemia have a poor prognosis, probably not because their disease is more aggressive, but because of associated congenital abnormalities, poor tolerance of infection, and possible altered drug metabolism that makes appropriate treatment difficult. Modification of cytotoxic treatment to prevent treatment related deaths, however, is likely to lead to poor response to treatment so that the only effective approach to treatment is to give standard protocols with full supportive care and an

aggressive policy for detection and treatment of infections.

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Who's in CHARGE? Multidisciplinary management of patients with CHARGE association

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Abstract

Clinical experience of 50 patients with the CHARGE association is reviewed and problems with management of children born with multiple system involvement is highlighted. It was found that the outlook for survival was poor if more than one of the following three features was present: cyanotic cardiac lesions, bilateral posterior choanal atresia, or tracheo-oesophageal fistula. Mortality was largely due not to the structural heart defects or choanal abnormalities, but reflected underlying pharyngeal and laryngeal incoordination, which resulted in aspiration of secretions. Outcome is likely to be improved if collaboration between specialist surgical teams allows necessary procedures to be performed using the minimum number of anaesthetics. Examination of both the short and long term management of these children has stressed the importance of a multidisciplinary approach to their care.

CHARGE association was first described by Hall *et al* in 1979,¹ but the acronym CHARGE (Colobomata, Heart defect, choanal Atresia, growth and/or developmental Retardation, Genital hypoplasia, Ear abnormalities) was initially coined by Pagon *et al* in 1981.² Since then it has become clear that facial palsy, renal abnormalities, orofacial clefts, and oesophageal atresia frequently accompany the main features.^{3,4} Despite extensive description of the features that comprise the CHARGE acronym, there have been virtually no reports of the management, outcome, and survival of these patients. As the number of patients with CHARGE association who have attended this hospital far exceeds any published series, we felt it appropriate to describe our multidisciplinary experience in the clinical management of these patients. We also felt it important to consider, from all the clinical specialities that inevitably become involved in the management of these patients, which team should be in charge of organising long term care?

Patients and methods

The study comprised 50 patients with CHARGE association; 29 were boys and 21 were girls. All patients were referred from district general hospitals to one of the following departments within this institution: cardiology, respiratory medicine, gastroenterology, ear, nose, and throat, ophthalmology, and genetics. The criteria for inclusion in this study required

that patients should exhibit at least four of the major abnormalities listed by Pagon *et al*.²

Detailed information on the precise range of abnormalities presented by each patient as well as their medical and surgical management was stored on an Amdahl mainframe computer. Data was analysed using an SAS statistical package and employing χ^2 and Kaplan-Meier actuarial survival analysis as appropriate.

Results

ACTUARIAL SURVIVAL ANALYSIS

Of the 50 patients with CHARGE association, 13 have died (nine boys and four girls). Actuarial survival analysis (fig 1) was 70% at five years and showed that, of those who died, most succumbed in the first year of life. Three patients died as neonates, seven died between 1 month and 1 year of age, and three died between 1 and 5 years of age. Seven of these 13 patients (54%) died of aspiration. Considering that a further five patients had either withdrawal of support or sudden death (cause unknown), aspiration of secretions may clearly represent the major incremental risk factor (table 1).

SURGICAL MANAGEMENT

Thirty two patients presented with cyanosis, which was due to congenital heart disease in 12, choanal atresia in 12, and to a combination of heart disease and choanal atresia in eight.

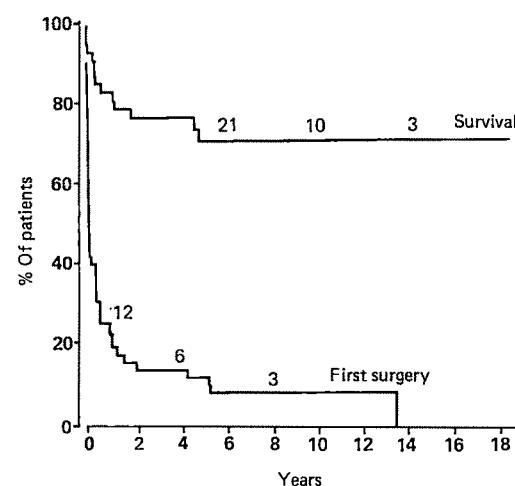


Figure 1 Upper curve: Kaplan-Meier actuarial survival of 50 patients with CHARGE association. Numbers along the curve portray how many patients were still being followed up. Lower curve: actuarial analysis of the time elapsed before each patient with CHARGE association required their first surgical procedure.

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Table 1 Details of children who died (*n*=13)

	No of patients
Died <1 month postoperatively	7*
Died of aspiration pneumonia	2
Decision to adopt no active treatment	1
Sudden death: cause unknown	3

*These seven children died from aspiration (*n*=5), disseminated intravascular coagulation from sepsis (*n*=1), and withdrawal of treatment (*n*=1).

The actuarial probability of patients with CHARGE association requiring at least one major surgical intervention is shown in fig 1. Twenty six patients (52%) required surgery as neonates (table 2). By 1 year of age nearly three quarters of the patients had undergone some form of major surgery and a further five have needed a general anaesthetic for 'minor' procedures.

The 50 patients in the study have so far required 114 major surgical procedures (average: 2.3/patient). Patients with bilateral posterior choanal atresia received proportionally more surgical procedures (2.8/patient) and investigations under general anaesthetic (4.7/patient) than the remainder who required only 1.6 surgical procedures/patient and 3.3 investigations/patient.

Only two patients have not required any surgery; in contrast, two patients have needed eight major operations. Although reoperations were predominantly for choanal dilatation, cardiac repair, or insertion of grommets, a number of patients required genitourinary, ophthalmic, or plastic surgery. Six patients underwent repair of cleft palate, three patients had operations for skeletal abnormalities, one needed aspiration of a cerebral abscess, and another required excision of occipital encephalocele.

Furthermore, there were 12 Nissen fundoplication operations for gastro-oesophageal reflux or formation of a feeding gastrostomy and seven patients needed a tracheostomy. Four patients required both operations and, although these four may have been expected to have the most severe defects, none of them had bilateral posterior choanal atresia.

Half of the children who survived more than one year had needed at least one operation for myringotomies, a third required microlaryngobronchoscopy (average of two repeats/patient), a quarter needed some form of eye surgery, and nearly a quarter of the boys had orchidopexy.

We found that patients with CHARGE association had a high postoperative mortality. There was no correlation with the type of surgery, but of those who died all had at least three general anaesthetics before death, including one patient who had 12.

It was not possible by retrospective analysis to predict with certainty those patients who represented a high operative risk (table 1) but certain combinations of features seemed to predispose to a poor outcome, particularly bilateral posterior choanal atresia combined either with cyanotic heart disease or tracheo-oesophageal fistula (table 3).

Table 2 Details of neonatal surgery (*n*=26)

	No of patients
Choanal atresia repair	10
Tracheo-oesophageal fistula	5
Cardiac surgery	7*
Tracheostomy	2
Inguinal hernia	1
Cutback for imperforate anus	1

*Four were palliative.

Table 3 Outcome

Abnormality or risk factor	Total No	Alive	Dead	% Mortality
Bilateral choanal atresia	16	9	7	44
Cyanotic heart disease presenting in first week	21	10	11	52
Bilateral choanal atresia and cyanotic heart disease	7	1	6	86
Tracheo-oesophageal atresia and fistula	5	2	3	60
Tracheo-oesophageal fistula and bilateral choanal atresia	2	0	2	100
Tracheo-oesophageal fistula and cyanotic heart disease	4	1	3	75
Given prostaglandin E2	8	1	7	87
Tracheostomy	7	4	3	43

CONGENITAL HEART DISEASE

Congenital heart disease was present in 42 (84%) patients; the other eight had normal hearts. The range of cardiac malformations varied but there was a preponderance of right sided lesions. Thirty patients had major congenital heart disease (defined as requiring surgery) (table 4), six of whom also had aberrant subclavian arteries.

Patent ductus arteriosus was associated with severe cardiac lesions in 19 patients: 13 were large enough to require surgical closure, five closed spontaneously, and in one patient, who subsequently died, it was not treated at the request of the parents.

Twelve patients had (haemodynamically) comparatively mild heart defects: either a small atrial or ventricular septal defect, pulmonary stenosis, patent ductus arteriosus, or a combination of these.

RESPIRATORY PROBLEMS

Twenty eight (56%) patients had choanal atresia or stenosis and 19 (38%) had no defect; three were not examined.

Sixteen patients had bilateral posterior choanal atresia (BPCA), and a high proportion of these (nine of 16, 56%) also had facial palsy.

Table 4 Range of congenital heart disease in patients requiring cardiothoracic surgery (*n*=30)

Congenital heart defect	No of patients
Tetralogy of Fallot	4
Fallot with AVSD	4
Fallot with Ebstein's anomaly	1
AVSD alone	2
AVSD with DORV	1
AVSD with TAPVC	1
Pulmonary atresia/VSD	2
DILV with SRAV and pulmonary stenosis	1
DORV with pulmonary stenosis and VSD	1
Pulmonary stenosis with aortic stenosis	1
Pulmonary stenosis and secundum ASD	1
TGA with pulmonary stenosis	1
VSD and PDA	2
VSD and secundum ASD	2
VSD with Ebstein's anomaly	1
VSD	2
Secundum ASD and PDA	2
Coarctation of the aorta and PDA	1

ASD, atrial septal defect; AVSD, atrioventricular septal defect; DILV, double inlet left ventricle; DORV, double outlet right ventricle; PDA, patent ductus arteriosus; SRAV, straddling right atrioventricular valve; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of great arteries; and VSD, ventricular septal defect.

Ten children with BPCA were alive at 18 months of age, all had severe feeding problems and exhibited a pronounced failure to thrive. They all required grommets, and all showed more severe developmental retardation than the children without BPCA. Of these 10 survivors, eight had inner ear problems ranging from severe sensorineural deafness to structural temporal bone defects, eight had gastro-oesophageal reflux of whom two required Nissen's fundoplication, four had laryngeal problems, and three needed a tracheostomy. Children with BPCA required more operations and investigations than the other CHARGE patients and, as a consequence, they spent substantially more time in hospital. In contrast, none of the nine patients who had either unilateral choanal atresia or stenosis died and only two of them required grommets.

Polyhydramnios can be a predictor for BPCA; of the eight children born to mothers with polyhydramnios, seven had BPCA.

EAR ABNORMALITIES

All 50 patients had abnormal pinnae or deafness, or both. Most patients (94%) had the typical external features of lop or cup shaped ears with a minority being low set only. In 34 (68%) the ear abnormalities were bilateral.

Two thirds of the patients had middle ear problems, consisting of ossicular malformations, stapedius tendon abnormalities or chronic serous otitis media, or both, resulting in conductive hearing loss.

Nineteen (38%) suffered inner ear abnormalities of the cochlear or semicircular canals resulting in severe sensorineural deafness, and 15 (30%) had severe mixed hearing loss; all required hearing aids.

Eight patients had cleft lip or palate, or both, and four of these had evidence of glue ears. Of the 28 children with choanal atresia or stenosis, 22 (78%) had bilateral external ear abnormalities.

OCULAR MANIFESTATIONS

Coloboma affecting either one or both eyes was detected in 43 patients of the 47 examined by an ophthalmologist. Of these, only 16 had iris coloboma (two of these 16 had partial defects shown on transillumination of the iris). Two patients had normal fundi with iris coloboma, but 28 patients had fundal colobomata with normal irides. There was one case of eyelid colobomata, which has not previously been reported in patients with CHARGE association.

Colobomata affected the posterior segment in 38 of the 50 patients, this was bilateral in 32 patients, and in all except nine eyes (in five patients) the optic disc was involved. Quantitative assessment of vision has been possible in 13 patients; we found acuity of eyes with disc coloboma varied from Snellen 6/9 to bare light perception. One patient had a retinochoroidal coloboma without optic disc involvement and vision was 6/5. Segmental hypoplasia of the optic nerve head was reported in four eyes (in all cases it was the patient's better eye) and their acuity ranged from 6/6 to 6/18.

Microphthalmos (considered to be part of the 'typical coloboma' spectrum in that the defect arises from incomplete apposition of the fetal fissure of the optic cup) was present in 22 of the 50 patients: it was bilateral in nine, right sided in six, and left sided in seven. However, it was predominantly mild with only two patients having eyes that offered no useful vision.

Nystagmus was present in 13 patients with visual acuity ranging from 6/9 to 'bare navigation'. Strabismus was detected in 16 patients (seven divergent, six convergent, and three variable). Refractive errors were common (myopia, hypermetropia, and astigmatism), and in eight patients there was more than two dioptres of anisometropia. Spectacles have improved visual performance in 10 patients.

Despite copious lubrication and lateral tarsorrhaphy, three patients with facial palsy had corneal scarring.

Retinal detachment as a complication of colobomata occurred bilaterally in two patients and, at the time of diagnosis, one eye in each case was already inoperable. Both of the fellow eyes have required vitreoretinal surgery with removal of the lens and silicone oil exchange with useful vision presently retained.

GENITAL AND ENDOCRINE ABNORMALITIES

Of the 29 male patients, 28 (96%) had external genital abnormalities including at least 25 (86%) with micropenis (two were not documented); 17 (58%) had bilateral undescended testis. Of 21 male patients over 1 year of age, 15 had growth retardation and cryptorchidism, two had growth above the 3rd centile and cryptorchidism, four had normal growth and descended testes. Full endocrine assessments have not been completed on all the older children in our study; however, one boy was found to be growth hormone deficient. Four of the boys over 9 years old were studied for gonadotrophin deficiency and all were found to have flat luteinising hormone releasing hormone responses and negligible testosterone rise to human chorionic gonadotrophin.

OTHER ASSOCIATED FEATURES

Renal abnormalities (malrotation, hydronephrosis, reflux) were present in 12 (24%) patients. Thirteen (26%) patients had laryngeal malformations (laryngomalacia, laryngeal clefts, abnormal aryepiglottic folds). Forty four (88%) had feeding problems and, of these, 20 (45%) had gastro-oesophageal reflux. Five patients (11%) had oesophageal atresia with tracheo-oesophageal fistula.

Skeletal abnormalities were present in 20 (40%) patients. Eleven patients had hemivertebrae or scoliosis; nine had abnormalities of the extremities, predominantly syndactyly or clinodactyly.

GROWTH RETARDATION

Eleven neonates (22%) had intrauterine growth retardation and all subsequently continued to be growth retarded. However, not all children with

Table 5 Details of patients over 1 year of age (n=34)

	Failure to thrive: height and weight <3rd centile (n=26)	Relatively normal growth: height and weight >3rd centile (n=8)
Feeding difficulties	24	4
Gastro-oesophageal reflux	15	1
Nissen's fundoplication	6	0
Larynx/pharynx problems	8	0
Facial palsy	15*	1*
No of major operations (minimum/maximum)	1/5	0/1
Average/patient	1.4	0.5

*Of the children with facial palsy and failure to thrive, all 15 had feeding difficulties and 10 gastro-oesophageal reflux; the one child with relatively normal growth had both feeding difficulties and gastro-oesophageal reflux.

postnatal growth retardation had poor intra-uterine growth. In the first year of life, 39 patients had growth retardation (defined here as weight falling to below the 3rd centile), four patients were not growth retarded, five died at less than 2 months of age, and two were too young for assessment. Of the 34 children over 1 year old, 26 (76%) had growth retardation and eight (24%) were on or above the 3rd centiles. Data relating to the clinical management of these 34 patients is presented in table 5.

DEVELOPMENTAL DELAY

Twenty six patients (52%) with CHARGE association had developmental delay; eight (17%) did not. Sixteen were too young for assessment. Of those with normal developmental none had BPCA. Of the eight children with normal development, seven had either colobomata or auditory problems but not both.

A variety of neurological signs were noted in these patients. Facial palsy was observed at or soon after birth in 21 patients (right in 12, left in seven, with two bilateral). Most palsies were congenital with only three being acquired. Nine patients had microcephaly (defined here as a head circumference below the 3rd centile when measured at birth). Of these nine, all had developmental delay but the converse was not found. We found no correlation between the severity of mental retardation and the presence of microcephaly. Eleven patients (22%) had abnormalities shown on computed tomography: eight had mild atrophy, one had an occipital encephalocele, one had agenesis of the corpus callosum, and one had communicating hydrocephalus. Fourteen patients (28%) had abnormal

findings on electroencephalography. The association between abnormal neurological findings, hypotonia, and facial palsy is shown in table 6. A number of patients were reported by their parents to have infantile spasms in the absence of any fever.⁵

Discussion

Management of patients with CHARGE association is a challenging task both for the general paediatrician and other specialist teams. Integrated management is vital if these children are to reach their full potential.

In our attempt to ascertain from hospital records a complete list of patients with CHARGE association, we found a surprisingly high number of children with two or three of the main features who could not be categorised as having CHARGE association under the current nomenclature yet clearly appeared to be of the same broad phenotype. They also exhibited many of the associated anomalies found in CHARGE association such as those involving the vertebra, kidneys, facial palsy, short neck, hypertelorism, and widely spaced nipples.

Diagnosis, although straightforward in patients with all six of the main features of CHARGE, can become more difficult in several ways. First, diagnosis of CHARGE association in a neonatal girl may be more difficult than in a boy because abnormalities of external genitalia do not occur. Therefore only five of the criteria for CHARGE are available, and growth retardation may not yet be apparent. This is where the other associated abnormalities, particularly facial palsy, may be of value in the initial diagnosis. Second, difficulties of diagnosis may also be encountered with a neonatal boy who has coloboma, micropenis, and low set ears but no heart defect or choanal atresia. A final diagnosis of CHARGE association would require specific subsequent confirmation of developmental retardation especially as none of his lesions in themselves would affect childhood development. For most cases, however, the typical facial appearance (fig 2) of lop/cup shape protruding ears and facial asymmetry should be enough to alert the general paediatrician especially if there is cyanosis or respiratory distress in the newborn. Most cases of CHARGE association have been sporadic but in some there is clearly a genetic component²⁻⁹ with both autosomal dominant¹⁰ and recessive¹¹ transmission having been reported. Although karyotypic analysis is generally reported as normal in these patients, it is important to identify any chromosomal abnormalities before making a diagnosis of CHARGE association as a variety of chromosomal abnormalities can occur in association with colobomata and choanal atresia. In view of the overlap between CHARGE association and the DiGeorge sequence, it is important to confirm the integrity of chromosome 22 and to evaluate for thymic and parathyroid dysfunction.¹²

For optimal management, the patient with CHARGE association should ideally be referred to a hospital that can undertake all areas of specialist treatment and management. This

Table 6 Association between abnormal neurological findings, hypotonia, and facial palsy

	Hypotonia	Facial palsy	Hypotonia and facial palsy
Abnormal computed tomogram (n=11)	6	5	4
Abnormal electroencephalogram (n=14)	11	8	7
Abnormal computed tomogram and electroencephalogram (n=7)	6	5	5
Deaths (n=13)	5*	6	1

*Of the eight children without hypotonia who died, two were hypertonic, three had unknown tone, and three normal tone.

Figure 2 Typical appearance of CHARGE association, particularly apparent are the low set, dysmorphic ears and facial asymmetry.



helps in long term follow up, benefits the parents, and most importantly it offers an integrated, multidisciplinary approach. In this way surgical management can unify with investigations that also require a general anaesthetic. This requires active coordination and cooperation between the appropriate specialities. In our series of patients it is probable that a more unified multidisciplinary approach could have reduced the number of general anaesthetics by at least 25% and this may have helped to reduced morbidity and possibly mortality. High postoperative mortality may reflect the laryngopharyngeal incoordination, which can be present even when there is no structural anomaly. Over half of the deaths in our series of patients were attributable to aspiration of secretions. It is clearly important to be aware of this risk when considering the postoperative management and to realise that most of these patients have complications after anaesthesia. The respiratory problems encountered in CHARGE association are secondary to the oro/nasopharyngeal, oesophageal, and cardiac manifestations. The most severely affected group were unable adequately to swallow their secretions. They required tracheostomies to avoid recurrent aspiration of secretions and, after this procedure, needed very frequent suction for a prolonged period of time.

CARDIOLOGICAL EVALUATION

We found that heart disease tended to be severe in CHARGE association. Tetralogy of Fallot and atrioventricular septal defects were the most common cyanotic cardiac defects in our group of patients and, as reported previously, patent ductus arteriosus was a common finding either alone or associated with more severe lesions.¹³ We did not find the high incidence of aortic arch anomalies cited by other authors.¹⁴

As in previous reports, however, conotruncal defects were prominent.¹⁵

For a blue neonate presenting at a referring hospital, once an oral airway is established and the child remains cyanosed the cause is likely to be cyanotic congenital heart disease. The infant should be stabilised and transported to a regional referral centre.

Neonates who were given prostaglandin E₂, usually at the referring hospital for cyanotic heart disease, had a high mortality (table 3). This poor outcome may reflect the fact that these patients were critically ill neonates. It was subsequently shown that three of these patients had high pulmonary blood flow, however, and in retrospect they should not have received prostaglandin during transfer. Conversely, some patients with restrictive pulmonary blood flow survived transfer without receiving prostaglandin.

Patients with CHARGE association may require an early shunt procedure before a later definitive repair. It may be possible to send patients directly for cardiac surgery on the basis of echocardiographic findings alone; however, cardiac catheterisation may be necessary to identify anomalous subclavian vessels or to rule out peripheral pulmonary stenosis, or both.

In our experience, parents may decline treatment if their child has multiple defects, even if in our opinion their child is likely to survive their cardiac surgery.

MANAGEMENT OF CHOANAL ATRESIA

Bilateral posterior choanal atresia is an uncommon congenital abnormality with an incidence of one in 5000–8000 live births and presentation is with cyclical cyanosis relieved by crying. If choanal atresia is unilateral, persistent nasal discharge occurs. Anatomically there is failure to develop patency between the nasal cavity and nasopharynx, which occurs between the 25th to the 45th day of embryonic life.

Once the diagnosis of choanal atresia has been confirmed, stabilisation of the neonate by oral airway should be followed by urgent transfer to a regional centre. Computed tomography has emerged as the diagnostic radiological procedure of choice in evaluating posterior choanal atresia.¹⁶ It gives the surgeon detailed anatomical information about the type of atresia or stenosis—that is, bony or membranous, unilateral or bilateral—and this clearly may influence the choice of surgical approach in repair of the lesion. In our experience the transnasal repair is far more satisfactory than the transpalatal approach. Nasal stents are usually required for six weeks and patients may require further dilatations to guarantee nasal patency. It is suggested that any child with abnormalities of the choanae has investigations for associated structural problems in other systems.¹⁷ As we found a close association between BPCA and chronic serous otitis media one could argue a strong case for prophylactic grommets.

It should be possible to scan the temporal bones and brain at the same time and so prevent a repetition of general anaesthesia for each of these procedures. There should be prompt

investigation for possible cardiac anomalies or tracheo-oesophageal atresia as either of these major defects, especially when associated with choanal atresia, carry a high risk of mortality (fig 1 and table 3). This attrition may be, in part, due to the fact that these children need a number of general anaesthetics very early in life.

EAR ABNORMALITIES

The initial assessment consists of examination of the tympanic membranes to exclude a middle ear effusion. Then brain stem evoked audiometry may be used to help assess the level of hearing, and computed tomography of the temporal bone is used to exclude ossicular or inner ear abnormalities.

The insertion of grommets for chronic serous otitis media may make an enormous difference to the quality of life, and needs to be undertaken early as the first two years of life are vitally important in the development of speech. Chronic serous otitis media was very common in patients with CHARGE association, and many required early myringotomies with insertion of grommets, which resulted in rapid improvement in language development and balance. Often three or four repeat procedures were necessary when they were older at a time when one would expect middle ear effusions to have disappeared. It is also important to recognise that, even in the presence of structural anomalies or sensorineural deafness, alleviating glue ear can be beneficial. Assessment by an audiological physician and the prescribing of hearing aids for the more severely deaf is essential. Involvement of the peripatetic teacher of the deaf at an early age will allow counselling for parents and offer better provision for educational needs.

OPHTHALMOLOGICAL REVIEW

An initial examination by an ophthalmologist may show an important ocular defect, alternatively it may detect a subtle coloboma with little relevance to ocular morbidity, but will aid the diagnosis of the CHARGE association. Anisometropia (a difference in refraction of more than two dioptres between eyes) and strabismus are both causes of amblyopia, which are potentially amenable to occlusion treatment. Regular six monthly review is advised for the children with structural abnormalities as complications can ensue, such as retinal detachment or corneal exposure. Early intervention with copious ointment lubrication and, where this is insufficient, lateral tarsorrhaphy, may prevent corneal scarring and even perforation. Assessment of visual function is important to maximise potential for education as spectacles or low visual aids may improve visual performance.

GENITOURINARY AND ENDOCRINE ABNORMALITIES

The presence of micropenis and undescended testicles makes the early diagnosis of CHARGE

association easier in boys. There has been a report of labial hypoplasia in two females over 15 years old but similar findings were not established in our series of 21 girls.

There appeared to be a direct association between growth retardation in the boys and bilateral undescended testis. This may be a consequence of more pronounced hypothalamic hypopituitarism in the group with cryptorchidism. Of those tested, however, growth hormone deficiency was only found in one patient. Follicle stimulating hormone and luteinising hormone deficiencies were found in three of our patients, but most have not had full assessments. Hypothalamic dysfunction has been suggested as a cause of the hypopituitarism,^{3 18} whereas other reports have described high concentrations of follicle stimulating hormone and low baseline testosterone concentrations indicating a primary gonadal dysfunction.¹⁹ Treatment for these particular problems is not universally accepted but administration of low dose androgens for a limited time has enhanced penile growth.²⁰

It is important to look specifically for structural kidney abnormalities that can be associated with reflux. We found that facial palsy was often present in patients with renal problems and the lesions tended to be on the same side of the body.

GROWTH RETARDATION

Feeding difficulties were a major feature in patients who failed to thrive. The diagnosis of gastro-oesophageal reflux was made by barium swallow but the inert nature of barium sulphate may underestimate the number of patients with reflux. Therefore pH study techniques would be more appropriate in patients with feeding difficulties. Pharyngeal incoordination was present in 14 of our patients and, in those who underwent microlaryngobronchoscopy, structural defects were often found (that is, clefts of the larynx or pharynx, short aryepiglottic folds, and laryngomalacia). Many mothers expressed difficulty in weaning the children to any form of lumpy solid food. Our findings indicate that facial palsy was associated with feeding problems or gastroesophageal reflux, or both, and could therefore be used as a useful predictor for these and also for failure to thrive.

DEVELOPMENTAL DELAY

Evaluation of visual and auditory systems is vital but, in our experience, is easily overlooked by surgical teams intent only on achieving survival from a major cardiac, choanal, or tracheo-oesophageal repair. However, if all handicaps can be defined early then steps can be made to locate the appropriate resources for education as well as giving the parents as much information as possible. The diagnosis of mental retardation should be made with caution in anyone with impaired hearing and vision as they are inherently understimulated. Deafness, if not recognised early, may present with delay in language; poor vision may cause delay in fine motor skills. Children with both defective hear-

ing and vision may present at an earlier date with delay in gross motor skills and problems with balance. In some cases they may even appear autistic. Mental retardation may be present but should only be diagnosed when the extent of the sensory deficit is known and when the child has been in an adequate educational programme. We found, as with others,²¹ that major strides in development were often made by patients with CHARGE association once parents realised that mental retardation was not inevitable and the potential of their children was explained fully. We therefore consider that mental retardation should not be used as one of the features of the CHARGE association. Instead, the term 'developmental delay' may be more appropriate.

Two patients attended special schools because of their small physique but relatively mild sensory impairment. It is interesting that when these children were first assessed developmentally (between 2 and 3 years old) they had extremely poor scores, particularly in language and fine motor coordination. Normal schooling seemed out of the question and the parents were advised of this. Subsequent assessments proved this to be wrong. Slow initial development may be a consequence of prolonged hospitalisation for major surgery in the first year of life combined with lack of active management for their sensory deficit.

WHO'S IN CHARGE?

Patients with CHARGE association require multidisciplinary management. This may be difficult to coordinate; surgical units receiving sick neonates would do well to have a check list of main and associated abnormalities to be investigated in dysmorphic children. Although initial presentation of new patients is likely to be for the management of congenital heart disease, choanal atresia and/or tracheo-oesophageal fistula, however, it seems inappropriate for cardiac or paediatric surgeons to coordinate long term management of these patients. In our experience patients with choanal atresia generally required more surgical procedures and investigations under anaesthetic. We would therefore suggest the specialist paediatric ear,

nose, and throat surgeon (as these patients are also likely to have chronic ear problems including hearing aid provision), the general paediatrician, and the district community paediatrician to be the most appropriate coordinators of multidisciplinary long term management of these patients.

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Iron in tubewell water and linear growth in rural Bangladesh

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Abstract

The growth of 694 children from rural Bangladesh was studied. Children drinking water containing >1 mg iron/l ($n=628$) were significantly taller than those drinking <1 mg iron/l ($n=66$): their mean (SD) height for age Z score was -2.10 (1.34) compared with -2.45 (1.24), $p<0.05$. This suggests that iron deficiency may contribute to growth retardation in poor communities.

Most underweight children in developing countries are short compared with international growth standards. Deficits in weight in relation to height are less common.¹ The origin of this height deficit is still debated but it is suspected that mineral and protein deficiencies may play a part.² There is little epidemiological evidence, however, to support this hypothesis.

In Bangladesh, most drinking water comes from shallow tubewells. In some places, depending on the soil characteristics, water coming out of these tubewells is heavily loaded in iron. This gives a bad taste and a bad aspect to water and makes it less suitable for cooking. Iron reduces water acceptability and is often thought to be a cause of diarrhoea because villagers are tempted to use unsafe surface water when tubewell water contains iron.

In this study we examined the nutritional impact of water loaded with iron and assumed that it would be associated with increased frequency of diarrhoea and malnutrition. Our findings, however, give more support to the role of minerals to promote growth than to the hypothesis we originally tested.

Patients and methods

This work is based on data collected for the evaluation of a water and sanitation project that took place near Mirzapur, in rural Bangladesh between 1984 and 1987. Handpumps, latrines, and hygiene education were provided to an intervention area with approximately 5000 population and compared with a nearby control area. For this analysis, data from the intervention area only were analysed. In this area all households had access to tubewell water and used it, at least for drinking.

Measurements of heights and weights for nutritional assessment were made on average every three months for children below 3 years of age and every six months for children aged 3 to 5 years. Children were weighed to the nearest 0.1 kg on a Salter scale, which was regularly checked against standard weights. Length for

children aged less than 2 years and height for older children were measured to the nearest mm.

Nutritional indices for weight for age, height for age, and weight for height were calculated in Z scores, representing the difference of an anthropometric measure with the reference standard from the National Center for Health Statistics expressed in standard deviation units.³

This analysis was made with data collected in 1986, as water was analysed for that year only. These data were collected on 694 children, with a mean age of 25 months at the first visit and seen 2.3 times on average. For 257 children (37%) only one measure was available. As children were seen a different number of times, the nutritional state of each child was represented by its average Z score over the year.

Iron content of water was measured by the phenanthroline method for ferrous iron.⁴ The list of households using each tubewell was made at the time when water samples were collected.

Results

Children from households getting their drinking water from a tubewell with a iron content higher than 1 mg/l (upper limit for drinking water according to the World Health Organisation⁵) were slightly heavier than other children and these children had a significantly higher height for age. Weight for height was almost identical between the two groups (table 1).

Table 1 Nutritional state of children according to iron content of tubewell water used by the household. Results are mean (SD) Z score

	Weight for age	Height for age	Weight for height
Iron content of tubewell water:			
<1 mg/l ($n=628$)	-2.28 (0.99)	-2.45 (1.24)	-1.06 (0.79)
>1 mg/l ($n=66$)	-2.08 (1.20)	-2.10 (1.34)*	-1.11 (1.01)

* $p<0.05$ compared with children drinking water low in iron.

Table 2 Height for age of children according to the iron content of tubewell water in different age categories. Results are mean (SD) Z score

Age (months)	Iron content of tubewell water	
	<1 mg/l	>1 mg/l
<12 ($n=216$)	-1.51 (1.10)	-0.94 (1.40)
$12-23$ ($n=119$)	-2.66 (0.86)	-2.18 (1.04)
$24-35$ ($n=133$)	-2.83 (1.05)	-2.19 (1.07)
$36-47$ ($n=117$)	-3.06 (1.08)	-2.67 (1.27)
≥ 48 ($n=109$)	-3.06 (1.10)	-3.08 (1.14)

Two way analysis of variance—main effects: iron, $F=7.91$ and $p=0.005$; age, $F=24.61$ and $p<0.0001$; interaction term: $F=0.68$ and $p=0.60$.

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Adjusting the effect of iron by two way analysis of variance for age, the number of visits, land holding or for the possession of a watch or a radio, or for the level of education of the household head did not reduce the strength of the association between the iron content of tubewell water and height for age.

The effect of iron water on height seemed to be more pronounced in younger children who, on average, were significantly less stunted (table 2). Yet a two way analysis of variance failed to show a significant interaction between age and iron content of water, which means that the effect of iron was not significantly greater in younger age groups.

Discussion

The association reported here between the iron content of drinking water and linear growth may be coincidental or due to some unknown confounding factors. Confounding, however, seems unlikely. Iron concentration in drinking water depends on soil characteristics and high concentrations occur in clusters of tubewells independently of other factors determining nutritional state. Age of the tubewell was considered as a potential confounder as tubewells with a high iron content were often old models installed by slightly better off families before the project started. However, adjusting for other socioeconomic indicators did not change the association between iron and height. In addition, each tubewell was usually used by several families of different socioeconomic status.

In this community diet is based on rice and contains virtually no animal protein. Presumably, most of these children were iron deficient, both as a result of a low intake and of a low absorption of iron. Iron coming from the tubewell was in ferrous form, which is likely to be well absorbed, especially if taken between meals. We suspect we observed on a quasi experimental basis at the community level, the growth promoting effect of iron, which has been recently reported from a clinical trial.⁶

Further studies are needed to confirm our findings. Other minerals present in the soil along with iron, and not iron itself, may have promoted linear growth. Our observations, however, support the hypothesis that the mineral content of the diet may be an important determinant of linear growth.

Dr A Briand was seconded to the International Centre for Diarrhoeal Disease Research, Bangladesh by ORSTOM, Institut Français de Recherche Scientifique pour le Développement en Coopération, France.

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The five year school medical—time for change

G C Smith, A Powell, K Reynolds, C A Campbell

Abstract

School medical records of 1000 children born in 1981 were studied retrospectively. They showed that once known medical problems and those screened for by the school nurse (hearing, vision, growth) were excluded, only 17 problems requiring treatment were discovered: speech (n=10), development (n=3), undescended testes (n=3), and phimosis (n=1). This indicates that routine screening by a nurse, backed up by selective medical examination by the school doctor, is efficient and effective.

In recent years the effectiveness of routine screening tests has come under increasing scrutiny and particular reference has been made to school medicals.^{1,2} School medicals have been in existence since the 1908 Education Act, although since 1959 there has been no obligation to perform these medicals at any particular age. This has left individual community health departments to initiate their own programmes

of screening checks at various ages. At present, in the North Staffordshire district all children are screened at the age of 5 years, on primary school entry. Before the examination a questionnaire is sent to the parents inquiring about any known medical problems or any worries they have regarding their child. The school nurse performs an audiometric assessment using pure tone audiometry, tests visual acuity using the Sheridan Gardner single letter cards (STYCAR), and measures height and weight. The school doctor then sees the child, ideally in the presence of a parent and performs a physical examination and a basic neuro-developmental assessment including speech. Until four years ago, children also routinely received a medical at the age of 16 years, before leaving school. This is now a selective medical for children known to have medical problems or those who are thought by the parent, teacher, or school nurse to warrant a medical. Again a parent questionnaire is sent before this selection process.

We wanted to discover whether the present

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Problems found in the study

<i>Problem found</i>	<i>Total No of problems</i>	<i>New problems</i>	<i>New problems needing treatment</i>
		<i>Detected by nurse</i>	
	(n=205)	(n=77)	
Ears/hearing	99	43	
Eyes/vision	66	13	
Growth	40	21	
		<i>Detected by doctor</i>	
	(n=345)	(n=78)	(n=17)
Chest/nose/throat	78	8	0
Speech	72	19	10
Soiling/enuresis	43	4	0
Behaviour/development/central nervous system	32	10	3
Skin	27	1	0
Abdomen/genitourinary	26	19	4
Dental	24	7	0
Orthopaedic	24	3	0
Cardiovascular	19	7	0

non-selective system operating in North Staffordshire was an efficient screening programme, or whether this should become a selective examination. We looked retrospectively at information gleaned from school medicals performed on a selected number of an annual cohort and in particular we were interested as to whether any important medical or developmental problems would be missed by a programme of selective medicals, thereby possibly delaying treatment in these children.

Method

In 1981 there were approximately 6140 new-borns in the North Staffordshire district. Records of 1000 children born in 1981 were looked at, the sample obtained by taking every fifth set of notes from the files. From these notes information was obtained from the main school medical record (10M), the parent's questionnaire, and the preschool health clinic record.

Follow up data was obtained from the school medical and hospital notes and the records of general practitioners.

Results

A total of 1000 school medical records were obtained for analysis of which 473 were for girls and 527 for boys.

In 979 medicals the parent questionnaire was returned and in 935 a parent attended the medical. No problems were reported in 333 (34%) questionnaires and in 279 (84%) of these no problems were found at the medical.

In total, 550 problems were discovered in 441 children and a breakdown of these is given in the table. Of the problems found, 395 (72%) were either known to a doctor (general practitioner, paediatrician), known to the appropriate therapist (speech therapist, orthoptist), or known to the parents and reported on the questionnaire.

The 155 new problems were found in 145 children as a result of the medical examination (see table). Of these problems, 77 (50%) consisted of hearing, visual, or growth problems, screened for by the school nurse.

The next most common new finding was speech difficulties and 10 of these were referred for speech therapy. Seven heart murmurs were reported, which were found to be innocent at

follow up. Included in the abdominal or genitourinary problems were 10 boys reported as having undescended testes of whom three have had or are awaiting orchidopexy. One other had phimosis and required a circumcision. The remaining reported problems were of constipation, vague abdominal pain, a hydrocoele, an umbilical hernia, and a suspected inguinal hernia, none of which required treatment. One child's parents reported on the questionnaire that 'sometimes her water could smell strong at night'. A urine specimen was taken and found to have a significant culture of *Escherichia coli*. No action was taken by the general practitioner until eight months later, however, when a further urinary tract infection occurred and investigation showed bilateral grade III reflux with renal scarring.

Ten behavioural and developmental problems were discovered; two were referred to a child psychiatrist but each attended only one session. One child was referred to an occupational therapist because of clumsiness.

Discussion

The routine screening of children at school entry is largely historical. Preschool health services have improved and general living standards, which in the past contributed to such diseases as tuberculosis, have similarly changed for the better. A rethink of policy regarding school health management is now necessary but as any changes meet with opposition we have critically examined all the positive findings in a group of children undergoing school medical examination and identified the eventual outcome.

Of the 550 problems found in our study, only 155 (28%) were newly diagnosed and 77 of them were picked up by the routine screening checks carried out by the school nurse. The remaining 78 were either minor problems (innocent heart murmurs, dental, mild asthma) or problems that could be identified at the time of selection, by discussion with the teacher and school nurse (speech, clumsiness, behaviour, development). If we consider the remaining medical problems requiring treatment that might be missed, these would consist of three children who needed orchidopexies and a circumcision for phimosis. The outcome of orchidopexy is less favourable at this age,³ and ideally undescended testes

should have been picked up at the examination performed at 6 weeks of age. Interestingly one of these boys had no previous records of examination, the second was reported as having both testes palpable in the scrotum at 6 weeks, while the third had in fact had a left herniotomy at 5 months of age but required a left orchidopexy aged 5 years. In addition we know of at least one child in our sample who has had an orchidopexy who was recorded as having normally descended testes at the school medical.

One suggested advantage of the present unselective system is that of parental reassurance. Also the presence of a captive audience of parent and child in school has potential opportunities for health education. It is arguable, however, that little real value comes from a 10 minute physical examination, in addition to the questionnaire and the nurses' screening checks.

It has been suggested that this medical may be used for neurodevelopmental assessment.⁴ However there are several difficulties with this. Firstly, children with appreciable problems will probably already have been identified by the age of 5. Secondly, because there is a wide variation of normal and many signs are 'soft' there is a danger of labelling a normal child as one with a problem. An additional factor to consider is one of time. Bax and Whitmore estimated that 15–20 minutes was required per medical.⁴ This would increase by between 50–100% the estimated 500–600 sessions per year presently required in North Staffordshire and in our

opinion would require justification that real benefit would accrue.

The results of this study provide further evidence that a policy of selection of children for medicals at school entry is a reasonable one. This should be performed one term after school entry to allow time for teacher assessment. The selection process would be preceded by the screening of all children for hearing, vision, and growth problems by the school nurse. A class review would then be carried out by a named school doctor, school nurse, and the class teacher with the aid of a questionnaire completed by the parents and the preschool records. Criteria for selection for examination by the doctor should include: poor preschool records, previously identified problems requiring follow up, concern expressed by the nurse or teacher, and parental request. By adopting such a policy school doctors would be freed from performing unnecessary medicals on healthy children without fear of missing any important problems and this would allow more time to be concentrated on children in mainstream schools with special needs.

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Isolated fructose malabsorption

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Abstract

A patient with isolated fructose malabsorption presented with diarrhoea and colic during the first year of life and subsequently responded to a fructose free diet. Fructose malabsorption has been implicated in some cases of irritable bowel syndrome in adults and may also be an infrequently recognised cause of gastrointestinal symptoms in children.

Fructose is a monosaccharide and a component of the disaccharide sucrose that is increasingly being used as a 'natural' sweetener in processed foods. It was previously supposed that fructose was absorbed passively, and thus specific malabsorption states should not occur as they do for sugars that require brush border enzyme systems for their digestion and absorption. A low capacity, oxygen dependent transport system for fructose alone has been shown in the small bowel,¹ which is independent of the high capacity system used when fructose is absorbed together with glucose.²

Fructose malabsorption is a cause of recur-

rent abdominal pain in adults³ but in children only a single case (diagnosed in a 12 year old) has been described.⁴ In addition, asymptomatic adult volunteers have been shown to be intolerant of loading doses of fructose.⁵ Fruit juices containing fructose have been implicated as a cause of 'toddler diarrhoea', but symptoms were thought to be more related to the sorbitol component of the drinks than the fructose they contained.⁶

We describe a case of isolated fructose malabsorption diagnosed in the first year of life.

Case report

A baby girl was the product of a healthy term pregnancy and the second child born to unrelated parents. Her birth weight was 4000 g and there were no serious neonatal problems. She fed poorly from the breast, so was given cows' milk formula complements from 2 days of age, and fennel or blackcurrant drinks from 1 week of age. She was changed entirely to formula feeds at 4 weeks and rice weaners were added at the age of 6 weeks.

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Between 7 and 12 weeks of age she was admitted to hospital twice with a history of screaming after feeds, but was discharged after observation without a specific diagnosis having been made. A diet that contained no cows' milk, and various medications produced no relief of symptoms. The screaming bouts continued and she was reported to be 'windy' and have abdominal distension, the attacks being worse after she had had orange juice and bananas. At 7 months she was still thriving (weight >97th centile) with no abnormal findings on physical examination. A stool sample showed reducing substances with a pH of 5 on ward testing, yet chromatography failed to identify a specific sugar. In view of the association of symptoms with fruit and fruit juices the possibility of fructose malabsorption was raised and further investigations carried out.

The results of breath hydrogen tests carried out when she was 8 months old using loading doses of 2 g/kg sugar orally are shown in fig 1. A loading dose of sucrose gave an increase in hydrogen production (>20 ppm) at 45 minutes but no symptoms. A higher peak was seen at 75 minutes after a loading dose of fructose; this was associated with symptoms of bloating and screaming. Lactose produced a small peak at 15 minutes suggestive of bacterial overgrowth, but this was not confirmed on culture of jejunal juice.

A jejunal biopsy specimen showed normal villous architecture and normal assays of disaccharidases (all values expressed as U/g protein): lactase 59 (normal 6–55), trehalase 27 (normal 10–80), sucrase 120 (normal 40–152), and maltase 403 (normal 130–456). The tissue activities of fructose-1-phosphate aldolase and

fructose 1, 6-diphosphate aldolase were 122 (normal 107–517) and 226 (normal 218–1330) $\mu\text{mol/min/mg}$ protein, respectively, and the ratio between these enzymes was 1.85 (normal 1.22–4.26). An intravenous loading dose of 2.5 g fructose failed to cause a fall in plasma glucose or phosphate concentrations, excluding the diagnosis of hereditary fructose intolerance.

After the introduction of a diet containing no fructose or sucrose there was a remarkable improvement, but her symptoms recurred immediately when she was challenged with fructose. The child remained free of symptoms when sucrose alone was subsequently added to her diet. Further bouts of bloating and screaming occurred after accidental ingestion of fructose. When she was challenged with 20 g fructose at 2 years of age, she developed colic and loose stools, but a satisfactory breath sample was not obtained.

She presented to the clinic again at 4 years and 9 months of age with a six month history of episodic abdominal pain and distension that was followed by bouts of offensive stools that scalded the perineum. She had continued to avoid fruit, but had generally relaxed her other dietary restrictions. Her height and weight remained above the 90th centile.

A challenge with 15 g fructose orally caused a bout of abdominal pain but no alteration in the appearance or acidity of the stool. Measurement of her blood fructose concentration showed a minimal rise compared with a normal response of 0.7–0.9 mmol/l at 30 minutes to one hour, confirming malabsorption of the sugar (fig 2). A dose of 15 g glucose produced a normal rise in blood sugar of 4.0 mmol/l at 30 minutes. A jejunal biopsy specimen again showed normal villous architecture and levels of brush border disaccharidases. The patient was again placed on a strict diet containing no fructose with good effect.

Figure 1 Patient's breath hydrogen response to 2 g/kg oral sugar loads at 8 months of age.

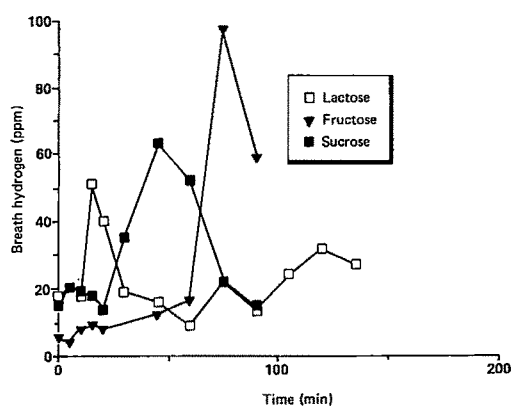
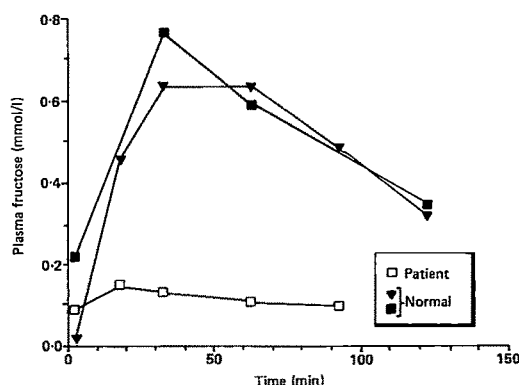


Figure 2 Response of patient at 4.8 years old compared with normal response to 2 g/kg load of oral fructose.



Discussion

Specific malabsorption of a monosaccharide can only occur if there is active transport of the sugar by the enterocyte. Although it was thought that fructose absorption was passive, Gracey *et al* showed an oxygen dependent transport system for fructose that was able to maintain a concentration gradient across perfused rat intestine.¹ Recently Rumessen and Gudmand-Hoyer, using absorption studies in human adults, have shown both a high capacity system that allows fructose absorption in the presence of free glucose, and a low capacity transport mechanism for the free monosaccharide that is selectively inhibited by sorbitol (a naturally occurring alcohol present in many fruit preparations).^{2,3,5} The high capacity system may simply represent solvent drag resulting from active glucose transport, and would explain the initially puzzling observation that adults who have fructose malabsorption can tolerate both sucrose, and fructose combined with glucose. The inhibition by sorbitol may, in part, arise from a negative osmotic effect on passive fructose absorption. This could account for the symptoms in a proportion of children with

'toddler diarrhoea' when given apple juice or other fruit drinks containing sorbitol.⁶

The incidence of clinical fructose malabsorption is uncertain. Rumessen and Gudmand-Hoyer showed that eight of 10 healthy adult volunteers failed to absorb 50 g of fructose, but only one of 10 failed to tolerate 15 g. They all absorbed 100 g of sucrose or a mixture of 50 g fructose and glucose. None had symptoms related to their malabsorption.² In a further study they showed malabsorption of fructose in seven of 10 adult volunteers who were given 5 g of fructose and sorbitol concurrently.⁵ A connection between 'irritable bowel syndrome' and fructose malabsorption has also been proposed. The same authors studied the absorptive capacity of 25 patients with functional bowel symptoms aged between 31 and 77 years, and found that 13 of the 25 showed abnormal breath hydrogen peaks and symptoms after taking 25 g fructose.³ The symptoms were made worse by the addition of sorbitol, but there was no reaction to sucrose or sorbitol alone.

Fructose intolerance—reproducible unpleasant symptoms in response to an oral challenge—does not therefore always follow fructose malabsorption. Our patient had both malabsorption and intolerance of fructose but tolerated glucose. The child clinically tolerated sucrose, but showed an intermediate degree of sucrose absorption on breath hydrogen testing. Presumably the normal sucrase activity hydrolysed the disaccharide and liberated free glucose, which then facilitated fructose transport (as was shown in studies in adults).² This

suggests that the low capacity oxygen dependent transport system was defective in our patient.

Abdominal colic and chronic non-specific diarrhoea are common complaints in infancy and childhood. One similar case of diarrhoea secondary to fructose malabsorption has previously been described, but the diagnosis was not recognised until the age of 12 years, although the symptoms began in early childhood as did those of our patient.⁴ The apparently high incidence of this condition in adults, and its possible relevance to 'functional' bowel symptoms suggest that it should be more actively considered in children with these symptoms, especially if they follow the ingestion of fruits or fruit juices.

We thank Professor RDG Milner for permission to report this case, Dr CD Holdsworth and Dr PT Hardcastle for suggestions concerning the investigations, Dr T Cox for helpful comments and assay of intestinal fructaldolase activities, and Dr GL Barnes for further information about the previously reported childhood case.

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Dietary management of D-lactic acidosis in short bowel syndrome

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Abstract

Manipulation of carbohydrate intake was used to treat severe, recurrent D-lactic acidosis in a patient with short bowel syndrome. Dietary carbohydrate composition was determined after assessment of D-lactic acid production from various carbohydrate substrates by faecal flora in vitro. This approach may be preferable to repeated courses of antibiotics.

D-lactic acidosis is a well recognised, but rare, complication of short bowel syndrome and intestinal bypass surgery.^{1,2} To date, seven children have been reported in whom this disorder occurred as a complication of short bowel syndrome. Non-absorbed carbohydrate is fermented by colonic organisms, but lactobacilli when present, unlike most other bacteria, produce D-lactic acid, which cannot be metabolised

by D-lactate dehydrogenase. Absorption leads to a severe metabolic acidosis. Treatment has been directed at altering the colonic flora with antibiotics,^{2,3} or by administering a standard bacterial flora orally.³

Recently we have successfully treated a girl with this disorder by dietary carbohydrate manipulation alone.

Case report

After massive small bowel resection for a spontaneous small intestinal volvulus, which followed a vigorous session of disco dancing, a 9 year old girl was left with 14 cm of jejunum beyond the duodenojejunal flexure; the ileocaecal valve was preserved. After prolonged parenteral nutrition she was discharged, nine months later on a normal diet together with energy supplements given as sip feeds.

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Results of fermentation tests of faecal lactobacilli: concentrations of D-lactate and bromocresol purple reaction*

Carbohydrate source	Strain 1		Strain 2		Strain 3		Strain 4	
	D-lactate (mmol/l)	Bromocresol purple reaction	D-lactate (mmol/l)	Bromocresol purple reaction	D-lactate (mmol/l)	Bromocresol purple reaction	D-lactate (mmol/l)	Bromocresol purple reaction
Glucose	27	+	27	+	141	+	82	+
Sucrose	17	+	34	+	92	+	87	+
Fructose	15	+	34	+	92	+	66	+
Raffinose	15	+	6	—	2	—	34	+
Lactose	23	+	27	+	66	+	51	+
Maltose	23	+	97	+	102	+	51	+
Arabinose	6	—	6	—	7	—	6	—
Inositol	1	—	1	—	1	—	1	—
Xylose	11	—	8	—	12	—	46	+
Sorbitol	1	—	2	—	2	—	2	—
Starch	1	—	71	+	77	+	61	+
Base	1	—	2	—	1	—	1	—

Bromocresol purple reaction: positive (+) and negative (—).

Six months later, after visiting a funfair and eating large amounts of sucrose rich foods, she presented with severe ataxia, slurred speech, and confusion. Biochemical investigations showed a severe metabolic acidosis (hydrogen ion concentration 80 nmol/l, carbon dioxide pressure 2.3 kPa, and bicarbonate 8 mmol/l) with a high plasma D-lactate concentration (9.1 mmol/l; normally not detected); L-lactate was normal (1.1 mmol/l; normal range 0.6–2.2) and ethanol not detected. She was treated with intravenous sodium bicarbonate and recovered rapidly.

During the next year she had several identical episodes that were related to eating large amounts of sucrose. Eighteen months after her operation episodes were occurring two to three times per month and she was exhibiting growth failure.

Nutritional support was provided by a whole protein feed (delivered nasogastrically by continuous infusion) in which the carbohydrate was provided as glucose oligosaccharides (Isocal, Mead Johnson). Increasing the enteral feed to provide more than 30% of her energy requirement, however, again resulted in D-lactic acidosis.

Stool culture showed a pure growth of lactobacilli, but treatment with a variety of broad spectrum oral antibiotics was ineffective. This led us to investigate the D-lactate producing capabilities of her colonic flora in relation to various carbohydrate substrates in vitro, with a view to manipulating her dietary carbohydrate.

Methods

Two species of lactobacilli (*Lactobacillus fermentum* and *Lactobacillus acidophilus*) were identified in the patient's stool. Their ability to produce acid from different carbohydrate substrates was assessed in DeMan, Rogosa, and Sharpe's (MRS) lactobacillus broth⁴ in the presence and absence of a variety of carbohydrates (20 g/l). After incubation at 37°C for 48 hours, pH was tested with 2% bromocresol purple. Acid production was deemed to be present if the solution turned yellow (pH <6). Both organisms isolated from our patient fermented glucose, lactose, maltose, and sucrose, but there was no acid production from starch.

Further studies were undertaken to confirm that acid production in our test did indeed

reflect the ability of lactobacilli to produce D-lactic acid from differing carbohydrate substrates.

Four different species of lactobacilli, including those of the patient, were therefore cultured as before, and the pH tested after 48 hours. After a further five days incubation, cultures were filtered and analysed blind for D-lactic acid using an enzymatic kit for L-lactate determination, substituting D-lactate dehydrogenase for L-lactate dehydrogenase (Boehringer Mannheim).

Results

The results are shown in the table. Concentrations of D-lactate up to 141 mmol/l were obtained. A positive bromocresol purple reaction was present after 48 hours incubation in all solutions in which the D-lactic acid concentrations exceed 14 mmol/l at seven days, with no false positives or negatives. This confirmed that the bromocresol purple reaction was a valid screen for D-lactic acid production by lactobacilli.

DIETARY MANIPULATION

Our investigations confirmed the absence of D-lactate production from starch by the patient's *Lactobacillus* spp. The diet was therefore altered, such that carbohydrate was provided mainly in polymeric form, using Osmolite (Abbott Laboratories) as a nasogastric tube feed. This resulted in a dietary carbohydrate profile as follows: monosaccharide 1%, disaccharide 6%; trisaccharide 8%, tetrasaccharide 7%, and pentasaccharide (and above) 78%.

In the subsequent 30 months there have been no further episodes of D-lactic acidosis and no antibiotic treatment. Growth has resumed and the patient has remained well in full time education.

Discussion

D-lactic acidosis should be suspected in any patient with short bowel syndrome with recurrent acidosis, particularly when complicated by abnormal neurological signs. In 1983 Perlmutter *et al* showed that a reduction in dietary carbohydrate in children with short gut syndrome led to a reduction in plasma D-lactate

concentration.¹ Dahlquist *et al* were able to precipitate an episode of D-lactic acidosis in a patient with intestinal bypass surgery, by using a 25.08 MJ (6000 kcal) load containing 54% carbohydrate.⁵ Similarly, Rosenthal and Pesce described a recurrence of abnormal neurological signs, together with high D-lactate concentrations, in a patient in whom enteral feeds were substantially increased.⁶

Our studies show the importance of the nature of the dietary carbohydrate substrate in the production of D-lactic acidosis. Manipulation of dietary carbohydrate with strict control of monosaccharides and oligosaccharides was successful in our patient and preferable to repeated courses of broad spectrum antibiotics, which may alter the colonic flora in such a way

as to impair valuable colonic salvage of non-absorbed nutrients.

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Atopic eczema, hyponatraemia, and hypoalbuminaemia

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Abstract

We describe an infant with atopic eczema, treated with homoeopathic medicines, who presented with erythema and limb oedema. Concentrations of urinary and plasma sodium and plasma albumin were low. On conventional treatment he made a satisfactory recovery.

Atopic eczema affects 5-10% of children under the age of 5 years.¹ We report an infant with atopic eczema, treated inappropriately with homoeopathic medicines, who became seriously ill with deterioration of the eczema and associated metabolic complications.

Case report

A 6 month old boy presented to casualty with a one week history of generalised erythematous weeping skin and pronounced oedema of the limbs. His parents had refused hospital admission when seen four days previously. Since 1 month of age his skin had been dry and eczematous. Homoeopathic medicines were prescribed for his eczema by a registered homoeopath. The eldest of his three brothers who had mild eczema in infancy had received similar treatment. Conventional treatment was repeatedly declined by the family, apart from a one week hospital admission at 4 months of age with bronchiolitis and eczema. He had received nine different homoeopathic medicines before admission including a six centesimal (10⁻¹²) dilution of trace metals (iron and arsenic).

Biochemical investigations showed low plasma and urinary sodium concentrations of

121 mmol/l and 10 mmol/l respectively and a low plasma albumin of 11 g/l (no proteinuria). Activities of liver transaminases and alkaline phosphatase and concentrations of plasma urea and potassium were normal.

Treatment was given with 0.45% sodium chloride solution, repeated albumin infusions, and intravenous flucloxacillin and benzylpenicillin. Intensive local skin care was started with potassium permanganate baths twice daily. Initially an ointment containing 1% hydrocortisone and 3% clioquinol (Vioform-Hydrocortisone; Ciba) was applied and then changed to one containing 0.0125% flurandrenolone and 3% clioquinol (Haelan C; Dista) applied twice daily to affected areas. A cream containing 1% hydrocortisone and 2% miconazole nitrate (Daktacort; Janssen) was applied three times daily to the perineum, and Diprobace cream moisturiser (Kirby-Warrick) was used on all areas of the body every two hours. Skin swabs initially grew *Staphylococcus aureus* and β haemolytic *Streptococcus Lancefield* group A. Repeat swabs also grew *klebsiella* and *Escherichia coli* and thus the antibiotics were changed to ceftazidime and gentamicin.

The weeping, erythema, and oedema of his skin gradually subsided and progress was satisfactory, apart from an episode of rotavirus gastroenteritis. He was discharged after three weeks with normal plasma sodium and albumin concentrations. On review at 10 months of age, he is thriving with mild eczema, which is now maintained on daily baths using an additive containing 5% acetylated wool alcohols and 63.7% liquid paraffin (Oilatum Emollient; Stiefel), 1% hydrocortisone ointment, and Diprobace cream.

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Discussion

Acute exacerbation of atopic eczema with weeping red skin is usually caused by secondary infection and requires prompt treatment with appropriate systemic antibiotics. Hyponatraemia and hypoalbuminaemia are rare complications of atopic eczema and occur if weeping (exudation of serum) is chronic and persistent.

Recently the number of parents who seek alternative forms of treatment has increased with the growing popularity of 'natural' products. While homeopathic medicine has relieved some diseases,² in our opinion there is

little evidence to suggest it is helpful in atopic eczema. Thus caution is needed in the use of homeopathic medicines as the sole treatment for this condition. Severe exacerbations should be recognised and treated early by conventional medicines to avoid the risk of potentially life threatening complications.

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Growth failure secondary to moyamoya syndrome

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Abstract

We describe a boy who presented at the age of 7 years with short stature due to hypopituitarism. Six months after starting appropriate hormone replacement treatment at the age of 8 he suffered his first generalised convulsion. Further neuroradiological investigation led to the diagnosis of moyamoya syndrome.

Moyamoya is the arteriographic appearance of a filmy network of small vessels at the termination of the internal carotid artery. We describe a boy with hypopituitarism associated with moyamoya.

Case report

The boy presented initially to our hospital at 18 months of age with obesity and developmental delay. He was the fifth child of unrelated, white parents (maternal height 0 SD, paternal height -0.9 SD) and was born at term by spontaneous vaginal delivery. The birth weight was 3450 g and there were no perinatal problems. The developmental delay was thought to be due to lack of parental stimulation and a physiotherapy programme was devised with support for the family. At 3 years of age he was admitted to hospital for investigation of persistent lower limb weakness but biochemical investigation excluded a myopathy. The family subsequently failed to attend hospital appointments.

At 7 years he was referred to the endocrine clinic with short stature, small genitalia, and headaches. On examination he was moderately obese with weight on the 25th percentile and height well below the 3rd percentile (-3.1 SD). There were no dysmorphic features. Blood pressure was 95/60 mm Hg. Fundoscopy and visual fields to confrontation were normal. He was alert and cooperative but clumsy with reduced power and tone in the lower limbs with tendon reflexes preserved and flexor plantars. His penis was small and the testes were less than 1 ml volume.

Investigation showed a TW2 bone age of 3.4 years at chronological age 7.1 years. Anterior

pituitary function was assessed after intravenous injection of thyrotrophin releasing hormone (200 µg) and luteinising hormone releasing hormone (100 µg) with oral clonidine 150 µg/m². Fasting venous samples were taken at 0, 20, 75, 90, 120, and 150 minutes. Plasma cortisol concentrations were 456, 440, 155, 215, 347, and 469 nmol/l respectively. Peak plasma growth hormone concentration was 1.6 mIU/l at 150 minutes and the peak plasma luteinising hormone and follicle stimulating hormone concentrations were 1.3 IU/l. Plasma thyroxine was 44 nmol/l with an abnormal, sustained rise in thyroid stimulating hormone (2.0, 13.0, 20.0 mIU/l at 0, 20, and 75 minutes) indicative of hypothalamic pathology. The basal prolactin concentration was raised at 642 mIU/l. These results confirmed hypopituitarism. Posterior pituitary function was not affected.

Treatment with growth hormone and thyroxine was started at the age of 7.4 years resulting in a rise in growth velocity from 2.3 cm year in the four years before treatment to 9.8 cm in one year on treatment. At 7.9 years he suffered his first generalised seizure and an electroencephalogram confirmed epileptiform activity. A radiograph of the skull showed amputation of the dorsum sellae; computed tomography showed a shallow pituitary fossa and suprasellar calcifications with obliteration of the cisternae but no well defined soft tissue mass. The third ventricle was deviated slightly to the left side. The radiological findings were not considered to be sufficient for diagnosis but the possibility of a craniopharyngioma was discussed. The seizures were controlled with carbamazepine and a magnetic resonance scan requested to allow better definition of the suspected tumour. Subsequently the child developed worsening headaches and at 8.4 years of age was admitted to hospital with blurred vision, ataxia, and increased seizure frequency. A repeat computed tomogram confirmed suprasellar calcification with highly attenuating tumour like tissue in the suprasellar region, now also extending to the ambient cisterns with

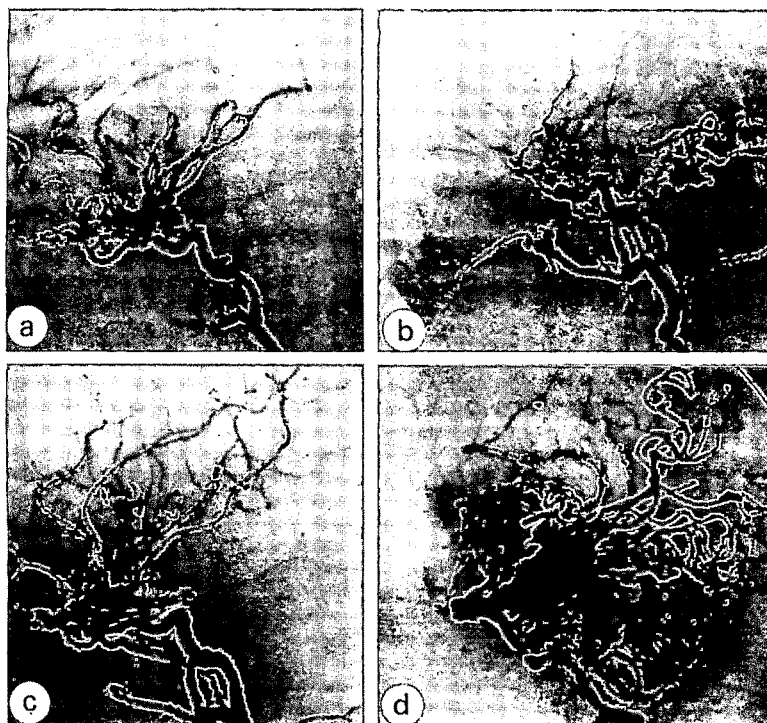
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Cerebral angiography (DSA) showing bilateral intradural carotid occlusion with moyamoya type of collateral circulation: lateral series of (a) left internal carotid, (b) left external carotid, (c) right carotid, and (d) left vertebral injections. Vascular territories recruited for collateral circulation include ophthalmic, posterior thalamoperforating, and posterior pericallosal as well as multiple meningeal vessels.

indentation of the posterior part of the third ventricle and obstructive hydrocephalus. The impression was that of a slowly spreading lesion in the cerebrospinal fluid spaces and in view of the apparently poor prognosis, growth hormone treatment was discontinued.

During this admission a ventriculoperitoneal shunt was inserted, and cerebrospinal fluid and plasma tumour markers were measured and all were normal (β human chorionic gonadotrophin, placental alkaline phosphatase, and α fetoprotein). Exploratory surgery at the age of 8.6 years showed a collection of abnormally prominent blood vessels in the sylvian fissure with a collection of tortuous arteries and arteriased veins. Subsequent cerebral angiography (figure) showed bilateral internal carotid artery occlusion distal to the origin of the ophthalmic arteries with a very extensive collateral circulation situated in the basal subarachnoid cisterns—so called moyamoya syndrome. The vascular nature of the 'tumour' and the absence of any other mass has subsequently been demonstrated by magnetic resonance imaging. The boy has been restarted on his growth hormone treatment and the thyroxine and carbamazepine continued. The family have been reassured of the absence of any malignant disease and advised that he should avoid contacts sports and extreme physical exertion as subarachnoid haemorrhage is a recognised complication.

Discussion

Growth failure as a consequence of hypopituitarism is not uncommon,¹ but we believe our patient is the first reported case of hypopituitarism associated with a moyamoya syndrome. Cerebrovascular moyamoya is the descriptive term applied to an abnormal blood vessel pattern on the base of the brain as a result

of stenosis or occlusion of the internal carotid artery,² usually bilateral, with development of a prolific collateral vascular network.³ It is the angiographic appearance that lead to Japanese authors referring to this as 'moyamoya', meaning 'puff of smoke'.

Similar neuroradiological appearances may be encountered with a variety of associated pathological entities. The syndrome has been reported in phakomatoses, septic infection of the head and neck, and tuberculous meningitis. Autoimmune diseases, peripheral vascular occlusive disease, head trauma, sickle cell disease, Fanconi's anaemia, intracranial aneurysm, arterial hypertension, brain irradiation, and chromosomal aberration have also been associated in reported cases.²⁻⁶ However, despite various hypotheses the aetiology of moyamoya remains unclear. The vast majority of cases, as in our case reported here, have no obvious cause for the vascular occlusion and the prognosis therefore can not be assessed on a firm pathological basis.

The exact association between the moyamoya syndrome and our patient's growth failure remains unclear but in view of the delayed bone age and pretreatment SD score of -3.1 it must be longstanding. As the initial computed tomogram showed a shallow pituitary fossa with suprasellar calcification, it seems likely that the space occupying vascular mass responsible for those appearances was also responsible for the pituitary dysfunction and growth failure.

We wish to acknowledge the help of the department of medical illustration at the Royal Hallamshire Hospital and Mr RDE Battersby for allowing us to report his patient.

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Staphylococcus epidermidis and retention of neonatal percutaneous central venous catheters

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Abstract

The percutaneous insertion of central venous catheters has become an established practice on many neonatal units. We describe four low birthweight babies, whose catheters became tethered in the vein, and discuss the management of this unusual complication.

Central venous catheterisation to facilitate total parenteral nutrition in sick very low birthweight babies avoids the need for repeated insertion of cannulas into peripheral veins. It also reduces the incidence of scarring associated with prolonged infusion of hypertonic solutions through small blood vessels.

Percutaneous central venous catheterisation, first described by Shaw in 1973,¹ is commonly used because it avoids the need for surgical insertion under general anaesthesia. We report four babies in whom a percutaneously inserted central venous catheter became retained in the vein, requiring surgical removal in two. We indicate the possible role of septic thrombus formation in tethering central venous catheters and suggest guidelines for the management of this complication.

Case reports

In each of the four cases described, a standard percutaneous central venous catheter was used (radio-opaque silastic central venous catheter, 0.3 mm internal diameter, 0.6 mm external diameter, Vygon Ltd) and all were inserted using strict aseptic technique. Catheter related sepsis was only conclusively diagnosed when the same organism was recovered from both the catheter and blood in an unwell baby. Microbiological assessment employed both semi-quantitative culture techniques (rolling the catheter tip across culture medium) and immersion in liquid broth, in an attempt to distinguish 'contamination' from 'true infection'.

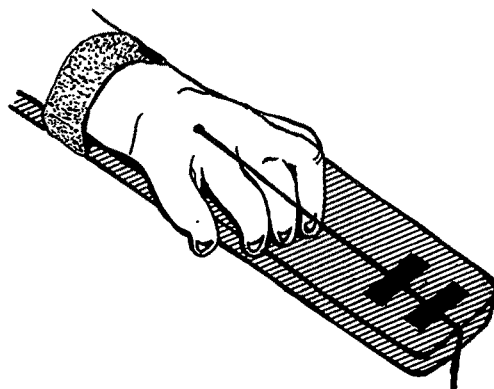
CASE 1

A boy, weighing 1705 g, born at 29 weeks' gestation suffered severe respiratory distress, bilateral pneumothoraces, and required a prolonged period of mechanical ventilation. To facilitate the administration of total parenteral nutrition, a fine silastic feeding catheter was introduced on day 17 through a vein on the left side of the scalp. The catheter tip was confirmed to be in the right atrium on radiography and intravenous feeding was uneventful until day 33 when *Staphylococcus epidermidis* septicaemia occurred and removal of the catheter was considered necessary. On moderate traction,

the catheter appeared tethered and firmer efforts led to the catheter snapping. By measuring the length of catheter removed, it was apparent that a 4 cm portion of catheter had been retained. The remnant could be palpated through the skin overlying the left side of the scalp, just distal to the original site of entry of the cannula. Through a small incision in the left temple, the remnant of the catheter was successfully removed and radiography confirmed complete removal of the cannula. On microbiological culture, both blood cultures from the infant and the retained segment showed a significant growth of *S epidermidis*.

CASE 2

The second of twin girls born at 29 weeks' gestation, weighing 1060 g, required prolonged ventilation for severe respiratory distress. A percutaneous central venous catheter was inserted via a vein on the dorsum of the right hand on day 12. The tip was confirmed to be in the right atrium on radiography and total parenteral nutrition was uneventful until day 25 when the infant became acutely unwell. There was slight erythema around the site of insertion of the catheter and its removal was considered necessary. The catheter, however, could not be withdrawn. Steady, continuous traction was applied to the catheter by pulling it to 'full stretch' and then taping it in this position to a splint attached to the baby's arm (figure). Every few hours, the catheter was 'restrapped' to maintain maximum traction. After 36 hours the catheter became free and complete removal was achieved. Blood cultures from the infant showed a significant growth of *S epidermidis*, but the catheter tip failed to show any growth in this case.



The splint traction arrangement.

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CASE 3

A percutaneous central venous catheter was introduced through a vein in the right antecubital fossa on day 24 of life in a girl born at 26 weeks' gestation weighing 700 g. The tip of the catheter was confirmed to be in the right atrium on radiography. After only five days, the infant became unwell and the limb became increasingly swollen and removal of the catheter was attempted. On traction the catheter offered firm resistance and then snapped leaving a retained portion. Radiography showed 7 cm of retained catheter, with the tip still in the right atrium and the proximal end fixed at the level of the deltopectoral groove. Surgical exploration at the latter site enabled the remaining catheter to be removed and complete removal was confirmed on radiography. Both the catheter tip and blood cultures from the baby yielded a significant growth of *S epidermidis*.

CASE 4

The first of triplets, born at 26 weeks' gestation and weighing 800 g, required prolonged ventilatory support. To facilitate total parenteral nutrition a silastic central venous catheter was introduced on day 30 of life. Having confirmed the catheter to be in a satisfactory position on radiography, intravenous feeding was uneventful until day 44 of life, when the infant became acutely unwell and removal of the catheter was considered necessary. The catheter appeared firmly tethered in the vein, however, and could not be withdrawn. Traction was applied using the splint arrangement described earlier, and after 18 hours the catheter became free and complete removal was achieved. Blood cultures from the infant and the catheter tip both yielded a heavy growth of *S epidermidis*.

Discussion

Although many neonatal units have probably observed retention and snapping of percutaneously inserted central venous catheters, we could find no reports of this particular complication in the literature and few guidelines on the management of this problem.

Recent papers have described the method of percutaneous silastic catheter insertion and reported other catheter associated complications—mainly occlusion of the line, infection, and limb swelling.^{2,3} In these reports the mean duration the catheters were in situ was 17 days² and 34 days.³ While sepsis was the most important complication, both studies reported a comparatively low incidence of catheter related bacteraemia (13% and 8%) compared with that from surgically placed catheters (18% infected).⁴ During the 18 month period in which these cases occurred, approximately 50 babies under-

went percutaneous central venous catheterisation in our hospital. Although we observed proved catheter related sepsis (same organism cultured from both catheter and blood) in at least two other infants during this time interval, we did not observe tethering of the catheter in any infant who did not show signs, both clinically and microbiologically, of *S epidermidis* septic-aemia. Retention of the catheter in our infants was not associated with a particular site of insertion. All the catheters were well within the manufacturers' recommended expiry date, and none were unduly difficult to insert. In none of our infants was the duration of cannulation as long as the mean duration reported in the above studies. Septic thrombus formation leading to tethering of the catheter in the vein seems a likely aetiological factor.

All of the infants described made a full recovery and fortunately none of the catheter remnants broke free into the circulation, where the potential complications might include massive intracardiac thrombosis, pulmonary embolism, erosion of the right atrial or ventricular wall with subsequent haemopericardium, and mycotic or bacterial endocarditis.

In the light of our experience with these babies, we would suggest that if a central venous catheter becomes tethered and cannot easily be removed, firm continuous traction using the splint arrangement described in the text may help to 'release' the catheter. If a catheter snaps, an immediate radiograph of the appropriate site will determine the position of the remnant (assuming the catheter is radio-opaque) and once the best site for surgical exploration has been decided, the retained segment should be removed as soon as possible. It is important to ascertain that complete removal of the catheter has been achieved after surgery—either by measuring the catheter pieces or repeating the radiograph. In larger infants it may be possible to retrieve catheter remnants from the large vessels and from an intracardiac site using cardiac catheterisation techniques⁵ and so avoid surgery. Finally, we would recommend notifying the manufacturing company, as they are always interested to examine any catheters that have 'behaved abnormally'.

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Cryptosporidiosis and acute leukaemia

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Abstract

Six children with cryptosporidiosis, concurrently receiving chemotherapy for acute leukaemia (n=5) and lymphoma (n=1), are described. Two died with evidence of persistent infection. Modification of the chemotherapy regimens in the other four children was associated with successful eradication of the pathogen and permitted continued treatment of the primary disease.

April 1989, six children treated in our department developed cryptosporidiosis. Five were receiving chemotherapy according to the Medical Research Council United Kingdom acute lymphoblastic leukaemia (UKALL) protocol, and the sixth had undergone allogeneic bone marrow transplantation for acute myeloid leukaemia. Patient details are as shown in the table. In all cases, oocysts of cryptosporidium were detected in the same local laboratory by a cold Ziehl-Neelsen technique.

Although the protozoal coccidian parasite, cryptosporidium, was first described as an animal pathogen in 1907, in more recent times it has been recognised increasingly as an important cause of diarrhoea in man. Surveys have shown it to be as frequent a cause of gastroenteritis as campylobacter, and more common than giardia, shigella, and salmonella. Cryptosporidiosis is a self limiting, although debilitating, disease in otherwise healthy people, but it may cause severe, intractable diarrhoea and malabsorption in immunosuppressed patients, and has been associated with a high mortality. Treatment with spiramycin, and bovine colostrum, has been used but with inconsistent results, and in the patient who remains immunocompromised, cryptosporidium has proved difficult to eradicate. Successful treatment has been documented in patients undergoing treatment for leukaemia, but at the expense of cessation of chemotherapy.^{1 2} Only one study has reported a spontaneous remission without alteration of treatment.³ However, this child was receiving an intermittent rather than a continuous chemotherapy regimen at the time.

We present our experience of the management of cryptosporidiosis occurring in children rendered immunosuppressed by antileukaemic treatment.

Patients and methods

Over the three year period from April 1986 to

Management and outcome

Of the six infected children presented here, four were managed by modification but not cessation of chemotherapy, and there was successful eradication of the pathogen. Two (cases 1 and 6) became chronically unwell with the infection, and were intolerant of continuous oral maintenance treatment. Transfer to a less immunosuppressive intermittent intravenous regimen, as described for the treatment of B cell non-Hodgkin's lymphoma, was associated with a rapid resolution of symptoms, decline in oocyst excretion, and improved well being, thus permitting continued treatment of their malignancy. Two further children (cases 3 and 5) did not exhibit such florid chronic symptomatology, and were managed successfully by stopping methotrexate, which is known to have associated gastrointestinal side effects. The remaining two cases died with evidence of persistent infection, despite cessation of immunosuppressive agents, confirming the potentially lethal nature of this pathogen.

Discussion

These cases represent the wide range of disease process that can occur, the severity being highly dependent upon host factors. By means of treatment modification in four of the cases the pathogen was successfully eradicated. In addition, all but one of our patients were treated

Summary of patient details, management, and outcome in six cases of cryptosporidiosis occurring in childhood leukaemia

Case No	Sex	Diagnosis	Age (years)	Management	Outcome
1	Male	T cell lymphoma	4.1	Spiramycin, changed to intermittent treatment†	Well. Off treatment 18 months
2	Male	Acute lymphoblastic leukaemia	4.5	Spiramycin	Died. Cryptosporidiosis and cytomegalovirus pneumonitis found at necropsy
3	Female	Acute lymphoblastic leukaemia	11.3	Spiramycin, omission of methotrexate	Well. Off treatment 12 months
4*	Male	Acute myeloid leukaemia	3.8	Nil	Died. Cryptosporidiosis found at necropsy
5	Female	Acute lymphoblastic leukaemia	1.8	Spiramycin, omission of methotrexate for 4 months	Well. Remains on treatment
6	Male	Stem cell leukaemia	1.5	Spiramycin, changed to intermittent treatment†	Well. Remains on treatment

All children, excluding case 4, treated according to the UKALL X protocol.

*Allogeneic bone marrow transplantation after chemotherapy with daunorubicin, cytosine and thioguanine.

†As described in the United Kingdom children's cancer study group (UKCCSG) non-Hodgkin's lymphoma maintenance protocol.

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with spiramycin. Portnoy *et al* reported symptomatic improvement in five of 10 immunocompromised infected patients, most of whom had the acquired immunodeficiency syndrome,⁴ and other anecdotal reports exist. In our cases, however, there was little evidence for the success of spiramycin alone, without manipulation of the chemotherapeutic regimen to reduce immunosuppression.

Neutropenia was an associated finding in most of our cases, both at presentation of the infection, and also on attempted reintroduction of oral treatment. One reason for this could be an increased toxicity from chemotherapy. Methotrexate exerts its greatest toxic effects on the gastrointestinal tract and the bone marrow. It has been suggested that gut damage predisposes to a greater enterohepatic circulation of methotrexate.⁵ This could produce further epithelial damage as a result of high intraluminal concentrations, aggravating a pre-existing enteropathy as might occur in cryptosporidiosis. This presumed increased enterohepatic circulation might conceivably lead to greater marrow toxicity as well.

Infection with cryptosporidium can occur by varied routes. Although primarily a zoonosis, with some cases traceable to infected livestock or domestic pets, person to person spread within families, day care centres, and hospital are well documented. More recently waterborne outbreaks have also been recognised.

No animal contact was established for any of our cases. Two of the children (cases 1 and 2) had overlapping admissions on the same ward, and may demonstrate nosocomial infection. In two further children (cases 4 and 5), asymptomatic excretion of oocysts was discovered after a prolonged period of hospitalisation, with previously negative stools, which might again suggest a hospital acquired infection. Although there were no other documented cases of

cryptosporidiosis on the wards at those times, the oocysts are known to be resistant to many commonly used disinfectants and may even survive for many months at 4°C. Thus in wards where care of immunocompromised patients is undertaken, special precautions should be taken with known cases of infection to help prevent nosocomial spread.

Minor outbreaks of cryptosporidiosis were documented in the Bristol district during the winters of 1987 and 1988. In neither outbreak could a specific source be identified (S F Gray, personal communication). Only case 6 falls within the time period of one of these outbreaks, and therefore might represent a community acquired infection.

In summary, cryptosporidiosis remains a life threatening infection in children who are immunosuppressed by chemotherapy, as documented by two deaths among the six cases described. Modification rather than cessation of chemotherapy regimens may lead to successful eradication of the organism, however, without leaving the child vulnerable to the primary disease.

We wish to thank Dr SF Gray for details of community outbreaks of cryptosporidiosis in the Bristol area, and the department of microbiology, Bristol Royal Infirmary, for help with laboratory diagnosis.

Dr ABM Foot is supported by the Alex Wolton Trust.

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CURRENT TOPIC

Monitoring and sudden infant death syndrome: an update

Report from the Foundation for the Study of Infant Deaths and the British Paediatric Respiratory Group

Apnoea monitors and sudden infant death were the subject of a report prepared for the Foundation for the Study of Infant Deaths and the British Paediatric Respiratory Group in 1985.¹ The evidence for and against respiratory monitoring and guidelines for the management and support of families issued with monitors were given. The five conclusions of that article were: (i) proof that some infants have a period of apnoea before irreversible brain damage occurs (the hypothesis underlying the use of the devices) is lacking; (ii) none of the respiratory monitors currently available is entirely satisfactory; (iii) the risk of recurrence of sudden infant death in a family is small; (iv) close supervision of, and support for, the families of infants being monitored is essential; and (v) apnoea monitoring does have a place, but only in selected circumstances.

Public awareness of the sudden infant death syndrome (SIDS) has continued to increase in the past few years; so too have parental demands and publicity for the use of respiratory monitors at home. Some of the more relevant work that has been published about monitoring and sudden infant death since the 1985 report is summarised in 'question and answer' form below.

Is there now evidence to suggest that there is a period of apnoea before death in SIDS?

The precise mode(s) of death in SIDS remain uncertain and unrecorded. Similarities between SIDS and apparently life threatening events for example, (near miss SIDS or apparent lifelessness) in which children may be found apnoeic, cyanotic or pale, and hypotonic, have been described. These episodes have various causes, mainly associated with the respiratory, cardiac, and central nervous systems, though the provoking factor of some remains undiagnosed. Apnoea during apparently life threatening events may be central, obstructive, or mixed.²⁻⁵ The distribution of intrathoracic petechiae and blotchy haemorrhages found at necropsy in many SIDS cases has been interpreted as a sign of negative intrathoracic pressure suggestive of upper airway obstruction.⁶ Functional collapse of the pliable pharyngeal airway during life will not be detected after death.

These apparently life threatening events occur in the same age range as SIDS and have the same male:female ratio. Many epidemiological characteristics of the two groups of infants are also similar. Infants with apparently

life threatening events do not, however, show the seasonal distribution of SIDS, and the episodes occur significantly less often between 2000 and 0800 hours.⁴ In the only population survey that we know of, nearly a third of the infants had further apnoeic episodes within three days of the first, but only 12% had a recurrence later.³ The inference must be that had the more serious episodes been unobserved sudden death could have resulted; it did occur in a small proportion later. Less than 7% of SIDS cases, however, had previous histories of apparently life threatening events.¹

Can infants who are at increased risk of SIDS now be identified?

The known epidemiological risk factors for SIDS (like physiological factors) are not considered significantly sensitive or specific, even in combination, to identify infants for particular intervention.⁷

There is no recent population based data for this country on recurrence rates among siblings. Figures from the United States,⁸ Norway,⁹ and Australia¹⁰ have recently been published. When matched for mother's age and birth order, the rate of SIDS in subsequent siblings of babies who died of SIDS in the state of Washington did not differ from that of controls.⁸ When Norwegian data were similarly adjusted for mothers age and parity, the relative risk for further sudden unexpected infant deaths was 2.8.⁹ In South Australia Beal and Blundell found that for most families (92%) the risk of recurrence was less than twice the expected risk. They identified a small subgroup (8%) with a significantly increased risk.¹⁰

Are more satisfactory monitors now available?

The monitors used at home in Britain are usually respiratory monitors, which detect only central apnoea. Cardiorespiratory monitors have been more widely used in Europe and the United States to detect the bradycardia that may accompany obstructive apnoea.

The Consensus Development Conference listed 12 'essential' and eight 'desirable' characteristics for impedance cardiorespiratory monitors.¹¹ The best available models fully met only seven, and partially met only two, of the essential characteristics. The three that were not met were the detection of obstructive and mixed apnoea and a minimum of false positive, or false

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negative, alarms. None of the eight desirable characteristics were fully met, and only two were partially met. The 1985 statement on monitors¹ listed the Graseby Dynamics MR10 Respiration Monitor, the Vickers Apnoea Alarm Mk 3 and mattress, the Eastwood Eastleigh Apnoea Respiration Monitor RE 200 (battery), RE 134 Apnoea Monitor (pressure pad) (mains), and the impedance systems (for example Healthdyne, Airshields, and Hewlett Packard). Their comparative advantages and disadvantages were described.

It was pointed out that none reliably identified cessation of respiratory air flow, including obstructive apnoea; all gave false alarms, and none incorporated a data storage system that would allow analysis of events preceding an alarm. The Graseby MR10, which is activated by abdominal movements, has been most widely used. The Densa monitor is similar in its applications, and its sensor is housed in an elastic belt that can be applied over clothing and can be easily moved without changing adhesive tapes on the skin if the position is wrong. The newer Densa monitor incorporates a supplementary alarm facility for minimum number of breaths/minute; this is aimed at the detection of irregular gasps that may occur during obstructive breathing efforts, but again relies primarily on abdominal movements. Rapid obstructive breathing efforts could not be expected to activate the alarms on either the Graseby or Densa monitors.

All impedance monitors are more expensive than other forms of breathing movement detectors. More recent Healthdyne models co-ordinate alarms that are activated if breathing movements and heart rate coincide at low rates, so avoiding failure of the alarm if there is a forceful cardiac impulse during prolonged central apnoea. Although theoretically less likely, body movements and some partially obstructed breathing efforts may still activate the respiratory channel in individual infants. A modified 'respiration index' detector system is being promoted as part of an alternative impedance monitor recently introduced as Atlas AR800 by the British Technology Group; although theoretically a useful advance, large trials are still required. The necessary application of electrodes to skin, and dependence on AC power supply, are potential disadvantages.

The detection of hypoxaemia by monitors has only recently been considered for use at home. Though transcutaneous oxygen monitors are unsuitable for long term unsupervised use outside hospital, pulse oximetry has the advantages that the probe needs less frequent changing and reliability is less affected by skin texture. Overheating and pressure necrosis of the skin have been described, however, and reliability in active infants is still under study. Poor quality of pulse signals during movement of the probe on a limb may compromise the monitor's usefulness in measuring both oxygen saturation and pulse rate during episodes of obstructive breathing. The Nellcor device with simultaneously recorded electrocardiogram seems to reduce the incidence of false alarms, but the necessary application of chest electrodes

is a disadvantage. The oximeter most commonly used in the United Kingdom is the Ohmeda.

An ambitious scheme of monitoring has been developed by Johnson *et al* in the United Kingdom. It is 'based on pulse oximetry and inductance plethysmography, but (is) also able to detect body movements and temperatures (body and ambient) and accept signals from measurements of transcutaneous or respired CO₂ or O₂, and pneumotachograph, ECG and EMG measurement for more detailed studies'. This can sample, partly analyse, and store data, which can then be transferred by telephone to a computer so that there is a two way link.¹² It is being used experimentally in the home.

Acoustic monitors designed to detect breath sounds, and to register apnoea if they are absent, have been described but are impractical for clinical use as are airflow detectors placed in the upper airway. Video recorders, infrared movement detectors, and other equipment used as monitors in research studies are also impractical because they require constant supervision, are too complicated for use at home, or are prohibitively expensive.

What is known about the beneficial or harmful effects of monitoring at home?

Many families who have had a sudden, unexpected, and unexplained infant death are made less anxious after the birth of a subsequent child if a respiratory monitor is available as part of a comprehensive support service; for others the devices increase anxiety. Adequately conducted studies on the psychological effects of monitoring are few, but the results suggest that some stress is always present.¹³⁻¹⁵ This important aspect needs more careful study of larger numbers of families. The 1985 statement,¹ and the recent United States National Institutes of Child Health and Human Development sponsored Consensus Development Conference on infantile apnoea and home monitoring,¹⁶ emphasised that adequate professional support services for families using home monitors were essential.

Which infants should be monitored at home?

Infants who have been found apnoeic, cyanosed or pale, and hypotonic—an apparently life threatening event—are possible candidates. The decision will depend on the nature of the provoking event (if identified), and this too may suggest the need for specific treatment, the most useful form of monitoring, or both. If no cause is found, the issue of a respiration monitor often remains a subject for discussion between the parents and paediatricians.

The families of subsequent siblings of infants who died of SIDS may often be helped by a comprehensive scheme of alternative support. A small controlled trial assessed support measures for 100 self selected families of such infants. All of the families kept charts of the symptoms and had weekly visits from a health visitor. In addition either respiratory monitors or scales for daily weighing were allocated randomly. Both systems proved acceptable, but support from

and discussion about the infants with health professionals was a vital aspect of management.¹⁷ The Foundation for the Study of Infant Deaths is now funding a scheme that it hopes may ensure that all families receive adequate support with the care of such infants. The purpose of this programme (CONI, Care of the Next Infant) is to establish such support in districts where it is lacking, and improve its organisation in districts where it is available. It is hoped that the scheme will gradually become autonomous.

The conclusions reached by Milner in 1985 have not been substantially altered by recent research.¹ A respiratory monitor that relies on movement to detect apnoea such as the Densa or Graseby MR10 will detect absence of breathing movements more reliably and earlier than human observation alone. These devices cannot reliably detect obstructive apnoea and evidence currently available suggests that this is more likely to be a possible mode of sudden unexpected death than prolonged central apnoea. Conductance pad monitors (Eastwood RE 134, Eastleigh RE 200) of similar cost avoid attachments to the baby and may suit some families or infants better. It must be re-emphasised that the decision to use a monitor at home should be accompanied by the provision of adequate support for the families, instruction on the use of the device, and instruction on how to resuscitate the infant.

We thank Dr U MacFadyen for her contribution to the section giving details of monitors.

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PERSONAL PRACTICE

Management of acute upper airway obstruction in an intensive care unit in a district general hospital

G H Lear, S A McKenzie, H Boralessa

Severe croup and epiglottitis are common causes of acute inflammatory upper airway obstruction that should be treated in intensive care units. These conditions are potentially life threatening and require immediate and skilled attention. Once the patient has been intubated, the principal aspects of management are efficient maintenance of the airway and good supportive care, and as long as mishaps are minimised, full recovery should result.¹

There are not many paediatric intensive care units and those that there are, are often unable to accept transfers. The provision of paediatric beds in a district general hospital adult intensive care unit helps to overcome this difficulty, and has been advocated in a recent publication by the British Paediatric Association.² If general intensive care units are to accept children routinely, however, it is important that the quality of care received is adequate, and does not fall far short of that offered in a specialist paediatric intensive care unit. The management of acute upper airway obstruction is reasonably straightforward and should be confidently undertaken by any general intensive care unit that accepts children. Results from different units should be comparable, and could be used as a guide to the quality of care provided.

We present an account of our practice, and describe the results of a survey of five years' experience of the management of croup and epiglottitis in our general intensive care unit. We discuss the lessons learnt, and the implications for the organisation of facilities of children in general intensive care units.

Oldchurch Hospital general intensive care unit

This general intensive care unit serves one of the largest health districts in Britain, with a total population of 457 000 of whom 83 200 were under the age of 15 years in 1986. It has six beds, but only four are being used because of shortage of money. Although it is an adult unit, it admits more than 12 children a year.² Two cubicles are available, and in 1986 one of these was designated for paediatric intensive care. Parents are encouraged to stay with their children, and accommodation is provided. The unit is under the direction of a full time consultant anaesthetist who liaises with the referring consultant paediatrician about the care of each child on the unit; she is responsible for all the

main decisions. Two registrars in anaesthetics are resident round the clock. Some of the nursing staff are trained in intensive care, but not specifically trained in paediatrics, although inservice training has been made possible by rotating children's nurses through the unit.

Clinical presentation

For this discussion the definitions given below have been used. Epiglottitis presents as a respiratory illness with a short constitutional upset, the most striking feature of which is muffled stridor without cough. An oedematous, and usually extremely inflamed, epiglottitis is seen at laryngoscopy. The aetiological agent is *Haemophilus influenzae*, which is usually cultured from the blood. Croup (laryngotracheobronchitis) may be of viral or bacterial origin. The common viral croup is usually caused by the parainfluenza virus, and presents as an upper respiratory tract infection that progresses to a barking cough and harsh stridor. Bacterial or pseudomembranous croup presents in the same way,³ but is often accompanied by constitutional upset and at intubation copious pus can be aspirated from the trachea, and pathogens such as *Staphylococcus aureus* and *H influenzae* are grown.

Most children with severe stridor present directly to the accident and emergency department and are admitted straight to the general intensive care unit. Some are referred from neighbouring hospitals where intensive care facilities for children are not available (the longest journey being six miles), and some are initially admitted to the general paediatric ward and transferred to the general intensive care unit when they deteriorate.

Management

INITIAL ASSESSMENT

There is a well established protocol for admission. A child presenting to the accident and emergency department with severe stridor is seen by both the paediatric and anaesthetic registrars who perform a rapid clinical assessment, but without examining the throat. The child is then accompanied to the unit by a doctor equipped to resuscitate if necessary. The children's cubicle is prepared before arrival on the unit. This includes anaesthetic equipment, resuscitation trolley, a selection of laryngo-

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scopes, endotracheal tubes (cut to size), and accessories for difficult intubation. All equipment is checked daily.

Nowadays we do not take lateral neck radiographs or use mist inhalation or corticosteroids in the acute phase of the disease, as none of these has been proved to be of value.⁴ Nebulised adrenaline (1 ml of 1/1000 added to 5 ml of normal saline) is occasionally used as an emergency measure while preparations are made to intubate.

IMMEDIATE TREATMENT

The decision about whether to laryngoscope the patient is made jointly by the senior members of the paediatric and anaesthetic teams. If required, laryngoscopy is done under general anaesthesia with halothane and oxygen. Swabs from the upper airway and tracheal aspirate are taken for culture, and the trachea is intubated orally to relieve the obstruction. A nasogastric tube is passed, and venous and arterial access obtained. If a diagnosis of epiglottitis is made, the first dose of chloramphenicol is given immediately. The patient is now stable, and a nasotracheal tube is passed; the diameter must permit a leak when an inspiratory pressure of 25 cm H₂O is applied. The nasotracheal tube is attached to a Tungstall connector, which is secured to the patient's face by two 1 cm zinc oxide tapes. The connector is also fixed by its wire attachment to the patient's forehead, protected with paediatric felt, and further secured by a head band of sticking plaster 5 cm wide.

Safe intubation requires the skill of an experienced anaesthetist, who in this unit is at least of registrar status. Under conditions such as these unsuccessful intubation has not been reported in several series.⁵⁻⁸ In common with other authors we have found the presence of an ear, nose, and throat surgeon unnecessary.^{7,9}

Such a protocol should avoid the admission of a severely ill child to an inappropriate place (such as a busy paediatric ward) where severe deterioration and even death may occur.^{1,10} The only death from upper airway obstruction in this district during the five year study period occurred when a 23 month old boy with croup severe enough to cause cyanosis was admitted to an infectious diseases unit without paediatric supervision; he died six hours later.

INDICATIONS FOR INTUBATION

Laryngoscopy is undertaken in children with clinically severe upper airway obstruction. Useful indicators are the presence of exhaustion, increasing respiratory effort, and hypoxaemia not readily reversed by oxygen given by face mask or head box (assessed by colour, neurological state, and pulse oximetry). Small infants are intubated earlier, particularly those under 1 year of age, as are children with known upper respiratory tract disease such as subglottic stenosis, and those who had a prolonged period of neonatal ventilation. Laryngoscopy is deferred in children who do not have symptoms or signs suggestive of epiglottitis or bacterial croup, and who are only moderately stressed.

SUBSEQUENT MANAGEMENT

After intubation we establish the child on continuous positive airway pressure of 4–5 cm H₂O with inspiratory assist of 5–7 cm H₂O with a Servo 900C ventilator (Siemens-Elema). This reduces the work of breathing and minimises the effects of sedation. Sedation was initially by bolus doses of papaveretum and diazepam, with Althesin (alphaxalone/alphadolone—no longer available) for uncomfortable procedures. The intermittent sedation achieved, however, and the frequency of accidental extubation, led us to adopt continuous morphine infusion (0.01–0.02 mg/kg/hour) with additional boluses of chloral (35 mg/kg) if necessary every three to four hours through the nasogastric tube. Intravenous fluids are initially restricted to two thirds of maintenance requirements. Nasogastric feeds are usually introduced within 24 hours of intubation. Chloramphenicol (100 mg/kg/day) is given for epiglottitis. For bacterial croup, flucloxacillin and ampicillin are given initially, with adjustment later according to bacterial sensitivities. Most children who are intubated for viral croup also receive a broad spectrum antibiotic (usually ampicillin) for prophylaxis. Subsequent management is carried out jointly by the paediatric and anaesthetic teams.

We give dexamethasone (0.1 mg/kg/dose every six hours) during the 24 hours before extubation to children who have either been intubated for prolonged periods or who have been reintubated several times to try and reduce subglottic oedema. Nebulised adrenaline is used if the child has severe stridor after extubation.

Complications 1983–7

We examined the medical and nursing records of all children who were admitted to the general intensive care unit during the years 1983–7 with a diagnosis of croup (viral or bacterial) or epiglottitis.

During the five year study period a total of 66 children with acute upper airway obstruction were admitted, of whom 36 were intubated (table 1). A further 68 children were intubated for other reasons. *H influenzae* was grown from the blood in eight of the 12 cases of epiglottitis, and there were no instances of bacterial resistance to chloramphenicol. There were no definite cases of bacterial croup until 1987. The organisms involved were β haemolytic streptococcus group A, *H influenzae*, and in one case both *H influenzae* and *Streptococcus pneumoniae*.

Table 1 Number of patients admitted to the intensive care unit with each disease by year of admission

Year	Viral croup		Epiglottitis*	Bacterial croup*
	Total No	No intubated		
1983	8	4	1	0
1984	11	4	6	0
1985	10	1	3	0
1986	9	6	1	0
1987	13	6	1	3
Total	51	21	12	3

*All children with epiglottitis and bacterial croup were intubated.

Table 2 Characteristics of patients and summary of management

	Viral croup		Epiglottitis	Bacterial croup
	No observed	No intubated		
Total No of admissions	30	21	12	3
Mean (range) age (months)	57 (6-130)	47 (6-111)	33 (11-67)	25 (8-39)
Transfers from other hospitals	8	8	5	1
Median (range) length of stay (days)	1 (0-1-2)	3 (1-9)	3 (1-13)	4 (4-18)
Median (range) duration of intubation (hours)		36 (8-186)	38 (20-266)	72 (45-344)

Table 3 Complications in intubated patients

	Viral croup	Epiglottitis	Bacterial croup	Total No
Accidental extubation	6	3	1	10
Reintubation after failed elective extubation	3	1	1	5
Endotracheal tube block	4	2	0	6
Pulmonary shadowing	6	3	3	12
Urinary retention	4	6	1	11
Inappropriate secretion of antidiuretic hormone	2	2	1	5
Neurological abnormality at follow up	0	1	1	2
Others	4	2	1	7
Total No of patients with complications	13	11	3	27
Total No of patients without complications	8	1	0	9

The age ranges and duration of intensive management are shown in table 2. Twenty two patients were transferred from other hospitals, six having been intubated before transfer.

Complications occurred in 27 of 36 intubated patients (table 3). They could be divided into two groups—those primarily associated with management, and those primarily associated with the disease itself. Some (such as retention of urine) clearly fell into the former category, whereas others (such as pulmonary shadowing on chest radiographs) were of less obvious cause. Table 3 shows the numbers of patients who experienced each complication, and it is evident that some had multiple problems. Of the 36 children intubated, 14 had one complication, eight had two, and six had three or more. Only nine patients had uncomplicated courses. Seventeen patients had complications associated with their endotracheal tubes. Other acute complications were pulmonary oedema ($n=2$), one of which was associated with overt fluid overload, one apnoeic episode after the administration of papaveretum for sedation after intubation, one episode of bronchospasm probably as a result of aspiration, hypothermia after the initial intubation, and fluid overload leading to periorbital oedema. One child had a prolonged bradycardia after accidental extubation, and during a difficult reintubation went on to cardiac arrest from which he was successfully resuscitated. This child, who had bacterial croup, had a minor neurological deficit at follow up (mild weakness of one leg). The other neurological complication occurred in a child with *H influenzae* septicaemia who also had a difficult clinical course with inappropriate secretion of antidiuretic hormone and convulsions; he now has overall development delay. His previous development, however, was said to have been slow, and it is difficult to assess the part played by the acute illness. There were no deaths during this period.

Should a general intensive care unit admit children?

The number of patients requiring respiratory support for acute inflammatory upper airway obstruction in our unit was larger than those in two recent series.^{9 10} This may reflect the size of the catchment area, as demographic data for comparison are given in only one of these reports. The intubation rate/100 000 child population (less than 15 years old) each year in our district was 8.7, compared with 4.0 in Northampton. The intubation rates for epiglottitis were 2.9 and 2.7, respectively, and the difference may be the result of either a higher incidence of severe croup or of a lower threshold for intervention in our district. In 1987 we intubated 10 children for acute upper airway obstruction, and if this is typical of other districts the extra workload on a regional unit resulting from referral of these children would be considerable. The case for continuing to manage these problems in the district hospital is strong purely on numerical grounds.

Potential disadvantages of a general intensive care unit include the lack of trained paediatric nursing staff, the lack of specialist paediatric services, and the comparatively small number of children admitted.

Although only 36 children required intubation for upper airway obstruction during the five years of our survey, they remained intubated for a cumulative total of 93 days. Including other diagnoses, a total of 104 children required airway support during this period, which provided adequate experience for staff in the general intensive care unit to maintain their skills in caring for critically ill children.

Conversely, management in a local unit has some advantages over transfer to a paediatric intensive care unit. The journey itself may be dangerous in that the disturbance and anxiety caused to a child with one of these diseases may provoke acute obstruction, and even if intu-

Table 4 Number of patients experiencing problems associated with endotracheal intubation in previous series and in the present series

Series	Place where treatment carried out	No of intubated patients	Accidental extubation	Reintubation after failed elective extubation	Blockage of endotracheal tube
Schuller and Birk (1975) ⁷	Paediatric intensive care unit	86	9	16	Not recorded
Breivik and Klaatad (1978) ¹¹	University hospital	18	4	1	Not recorded
Schloss <i>et al</i> (1983) ⁸	Paediatric intensive care unit	118	6	Not recorded	3
Welch and Price (1983) ⁹	General intensive care unit	52	18	7	4
Present series (1988)	General intensive care unit	36	10	5	6

bated before transfer there is always the danger of accidental extubation. A longer journey for the parents may make visiting or living in a regional centre inconvenient—and sometimes virtually impossible if they are reliant on public transport, especially in rural areas. Local management allows for continuity of follow up in the event of complications.

If a general intensive care unit is to accept children its staff must be prepared to audit their results and to modify their management as necessary. Survival in our series was 100%, but the incidence of complications causes us concern.

Lessons learnt

MEDICAL

Several authors have described the complications of intensive management of upper airway obstruction in children, but most report only those associated with the respiratory system. Changes in chest radiographs are common and may be the result of the primary disease as well as of complications of management. The incidence in the present study compares well with those reported in several series.^{8 11-13}

We have compared our incidence of problems associated with endotracheal intubation with those in previous studies in both paediatric intensive care units and a general intensive care unit (table 4). This type of complication may well be under-reported, as it was notable in reviewing case notes for this survey that problems associated with intubation were often not recorded in the medical notes, and the true incidence was only appreciated after careful study of the nursing records. We found that accidental extubation was associated with the level of sedation achieved, and have recently changed our policy from the use of intermittent boluses of sedative to continuous infusion of morphine; we anticipate that this will give better control. The achieving of adequate sedation, however, also leads to problems; urinary retention was common, and 10 children required catheterisation. Acute retention may cause restlessness, which predisposes to extubation, and an indwelling urinary catheter should be used when necessary. Some authors have reported that nasotracheal intubation without sedation is well tolerated, but it may then be necessary to restrain the child to avoid extubation.^{6 14 15} The use of sedation thus represents a compromise. We feel that the disadvantages in terms of complications are outweighed by the advantages of reduced risk of extubation and of allowing the child to sleep

through the whole unpleasant experience, but we also recognise that we must attempt to find a more effective balance to reduce the incidence of urinary retention.

Fluid management should be carefully considered. Judicious fluid restriction is advisable initially as five of our patients had hyponatraemia and high urinary osmolality, which are indicative of inappropriate secretion of anti-diuretic hormone; in two others fluid overload was evident clinically, and in one patient it resulted in pulmonary oedema. This is a known complication of the relief of upper airway obstruction and should be anticipated.¹⁶

The long term complication rate was low, and again is comparable with previous studies.^{7 11} Most complications did not lead to serious problems, and the two patients with neurological effects had experienced stormy courses with cardiac arrest and repeated convulsions, respectively.

IMPLICATIONS FOR STAFFING AND EDUCATION

It is notable that only nine intubated patients did not have any complications at all, indicating that staff must be vigilant in detecting problems so that appropriate treatment can be started early to avoid deterioration. Planning is essential before embarking on the care of paediatric patients, and should include the establishment of a good working relationship between consultant paediatrician and anaesthetist, an understanding that junior staff are to be resident on—and dedicated to—the general intensive care unit, and provision for cover for the absence of senior colleagues. Senior paediatricians and anaesthetists should visit the unit daily, to avoid errors in management such as unnecessary delay in elective extubation.

The continuing education of nursing and medical staff is a necessary aspect of intensive care in the district, and inservice training should be provided. Paediatric intensive care is stressful for junior staff, and consultant staff must be prepared to give adequate supervision and support; this may represent a problem where the sites are split.

As with any child in hospital, the critically ill child on the general intensive care unit must be cared for by staff who appreciate the needs of the child. Although specialist children's nurses are preferable, we have found that nursing staff need not be specifically trained in paediatrics to acquire the necessary skills, and that the atmosphere on the general intensive care unit is calming and pleasant for both child and parents. At least one parent is encouraged to be present at

all times. The relief of anxiety is of particular importance in the management of airway obstruction.

Conclusion

Despite having encountered a number of problems we now feel confident in the management of upper airway obstruction in a district general hospital intensive care unit that caters for a mixed adult and child population, and which in 1987 admitted 53 children under the age of 15 years.

The requirement for paediatric intensive care exceeds the provision of facilities in specialist paediatric intensive care units, and the British Paediatric Association Working Party recommendations must therefore be implemented.² We stress the importance of the phrase 'identified general intensive care units', which implies that paediatric intensive care should perhaps not be attempted in every general intensive care unit but limited to those with appropriate facilities and strong motivation of senior staff. We cannot agree with the implication in a recent editorial that the 'occasional' child could be looked after safely in district units.¹⁷ By concentrating efforts in designated general intensive care units, sufficient numbers of children should be managed to ensure that skills are maintained and that inservice training is available.

The incidence of complications associated with endotracheal intubation in the manage-

ment of upper airway obstruction might be used as an 'indicator' in the audit of paediatric intensive care in a general intensive care unit provided that each incident is honestly documented.

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NEONATOLOGY—THEN AND NOW

Central nervous system investigation (1961)

Systematic ventriculographic studies in infants born with meningomyelocele and encephalocele. The incidence and development of hydrocephalus

JOHN LORBER

Department of Child Health, University of Sheffield (Arch Dis Child 1961;36:381-9).

Perhaps the interest in spina bifida has waned with the incidence falling so dramatically after the introduction of antenatal detection and termination of pregnancy. However, this paper offers an opportunity to contrast the methods of investigation of the central nervous system between the 1960s and the present day. The case material comprised 172 infants with neural tube defects. They were all under 9 months of age (23 over 8 weeks old) and were studied to determine the incidence of hydrocephalus.

'The main method of investigation was ventriculography, which was often associated with dye penetration studies and sometimes with pneumoencephalography'. 'Ventriculography was performed through the right side of the anterior fontanelle'.

The conclusions were that: (1) There was an 80% incidence of hydrocephalus with meningomyelocele and encephalocele. (2) This was highest with lumbar lesions and when paraplegia was present. (3) Repair did not influence the development of hydrocephalus. (4) These diagnostic studies should be done as soon as possible so as to assess prognosis and as a guide to treatment.

Today. Within a remarkably short space of time non-invasive techniques have replaced these difficult and potentially hazardous procedures. Brain imaging, fontanometers,¹ and the assessment of cerebral blood flow have almost eliminated the need for invasive procedures. Ventricular puncture is, however, still required but is a skill which, like the others replaced by surface monitoring, is less likely to be acquired by trainees in neonatology except, of course, in the parts of the world where modern expensive techniques are still unavailable. Even diagnostic lumbar puncture is, for good reason, being discouraged.^{2 3}

Trainee neonatologists should take the oppor-

tunity, should it arise, of learning how to do ventricular taps as they are at times still required for the detection of haemorrhage or infection or for the reduction of intracranial pressure. Unfortunately, as it has been pointed out by others, duty rotas today are such that a trainee may reach the point of applying for a consultant post with little or no experience of this procedure.

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John Lorber's first interest was in biochemistry, and he came from his native Hungary to Cambridge as an unpaid research worker in 1938 while still a medical student. He spent his whole paediatric career in Sheffield, starting as a research assistant and rising to become Professor and Head of the University Department of Child Health, retiring in 1981. He has always professed his main interest to be in 'ordinary' non-technical clinical paediatrics and his early interests were in tuberculosis and rheumatic fever. He is, however, best known for his contributions on the subject of neural tube defects. Such an authority did he become that patients were sent to him from all over the world and he has researched and written widely on this subject. He has contributed to numerous books and despite now being well into retirement is joint editor of a new book on *Anomalies of the Foetal Head, Neck and Spine*.

He was founder member and first Chairman of the Medical Committee of the Association of Spina Bifida and Hydrocephalus and was invited to organise many similar associations abroad. He has travelled widely as visiting professor with WHO and by private invitation, notably on two occasions being the Harvey Cushing Society of Neurology (USA) lecturer. Many will recall his opening paper of the 50th Anniversary of the BPA entitled 'Is your brain really necessary?' It is not surprising that his exceptional contribution to paediatrics has been recognised by many honorary memberships of learned societies, notably the Society of Research in Hydrocephalus and Spina Bifida and the BPA.

C H M WALKER

LETTERS TO THE EDITOR

Early complications of diabetes mellitus

SIR,—Dr Gibb and her colleagues have described in detail their findings of early physiological changes of renal function in children with type 1 insulin dependent diabetes mellitus (IDDM).¹ They conclude that an abnormally raised urine albumin excretion is associated with a high glomerular filtration rate and that serial follow up of these early markers is required to study their predictive roles in the development of nephropathy in IDDM. My concern regarding this statement is the suggestion that the measurement of glomerular filtration rate should be routine in children with diabetes.

Both glomerular filtration rate and renal plasma flow increase significantly with a variety of hormonal and metabolic disturbances. These include hyperinsulinaemia, hyperglucagonaemia, increased concentrations of circulating growth hormone, hyperketonaemia and hyperglycaemia.^{2,3} The effect of glycosuria on the glomerular filtration rate measurement is erratic and influences the analysis of renal plasma flow when estimated by para-aminohippurate (RN Dalton, C Turner, SA Greene, *et al.* Abstract presented at meeting of the Renal Association, 1987).

The subjects in the study of Gibb *et al* had diabetes of several years' duration and all had poor diabetic control with glycated haemoglobin (HbA_{1c}) 11.2 to 13.4% compared with a normal range of 5.0 to 8.0%. The measurements of the glomerular filtration rate were undertaken after breakfast which, from their description, almost certainly contained a considerable amount of carbohydrate. It is therefore likely that the blood glucose concentration during the glomerular filtration rate measurement period was abnormally raised resulting in glycosuria. Therefore, the design of their study may account for the abnormally raised glomerular filtration rate and the observation of a normal size kidney assessed by ultrasonography. I would contest that if glomerular filtration rate is to be measured in diabetic children, an attempt to standardise the metabolic milieu is necessary. Such manoeuvring would make routine measurement of glomerular filtration rate a difficult procedure for most paediatricians.

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- 1 Gibb DM, Dunger D, Levin M, Shah V, Smith C, Barratt TM. Early markers of the renal complications of insulin dependent diabetes mellitus. *Arch Dis Child* 1989;64: 984-91.
- 2 Greene SA, Dalton RN, Turner C, Haycock GR, Chantler C. Hyperglycaemia with and without glycosuria: effect on insulin and para-amino hippurate clearance. *Kidney Int* 1987;32:896-9.
- 3 Sandahl-Christiansen J, Frandsen M, Svendsen PA, Gammelgaard J, Parving H-H. Rapid changes in kidney function - factors influencing kidney function in diabetes and normal man. *Acta Endocrinol (Copenh)* 1981; suppl 242:11-3.

Dr Gibb comments:

Dr Greene suggests that complicated and invasive clamping techniques be used to standardise the metabolic milieu of children with IDDM before the measurement of glomerular filtration rate. He suggests that glycosuria may cause the observed hyperfiltration in these children. We measured glycosuria throughout the glomerular filtration rate procedure in these children, and in accordance with his statement that the association with glomerular filtration rate is 'erratic' we observed no correlation at all between the two variables.¹ Furthermore, in our children, glomerular filtration rate measurement when repeated a year later was remarkably consistent and the association with urine albumin excretion and renal size remained.²

The predictive value of hyperfiltration in IDDM cannot be determined from cross sectional studies and our one year follow up results merely confirm associations noted at baseline. We therefore suggested that much longer follow up is required to determine the predictive value of hyperfiltration in diabetes. At no stage did we state or suggest that glomerular filtration rate should routinely be performed on all children with IDDM. At the present stage of knowledge, this would be quite wrong outside the research situation.

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SIR,—We would like to add our comments to the recent report of Gibb *et al* on early markers of renal dysfunction in diabetic children.¹

Using two consecutive overnight urine collections we measured urinary albumin excretion in 64 type 1 diabetics, expressing the results as the geometric mean of the urine albumin creatinine concentration ratio (UA/UC). The diabetic children (34 girls) ranged in age between 4 and 18 years, with duration of disease from 6 months to 14 years and did not show any evidence of clinical diabetic nephropathy. Fourteen out of these 64 patients (22%) showed UA/UC values above the normal range (obtained in 57 matched healthy controls): this prevalence is similar to that found by Dr Gibb *et al* and by other authors, but greater than in other recent reports.² At variance with the results of Dr Gibb *et al*, all the prepubertal diabetics showed normal UA/UC, while all the children with increased UA/UC were older than 13 years: four out of these 14 subjects were at Tanner stage 2 and 3, while 10 were at stages 4 and 5. The patients with increased UA/UC had significantly higher mean four year values for glycated haemoglobin (HbA_{1c}) than matched subjects with normal UA/UC (mean (SD) 11.2 (2.5) compared with 8.1 (2.3); $p < 0.001$), confirming a strong association between long term glycaemic control and microalbuminuria. Moreover, we have measured glomerular filtration rate in 38 children with diabetes duration greater than five years, using ^{99m}Tc diethylenetriamine pentacetic acid (DTPA), a feasible and convenient method of assessing renal function in children³: in contrast to the findings of Dr Gibb *et al* we were not able to demonstrate any significant difference in glomerular filtration rate between the diabetics with normal

and those with increased urinary albumin excretion (130.6 (4.31) compared with 133.2 (3.29) ml/min/1.73 m²).

Nevertheless, in agreement with the data of Dr Gibb *et al*, no significant linear correlation was observed between glomerular filtration rate and either UA/UC or diabetes duration. A weak correlation ($p < 0.05$) was found between glomerular filtration rate and mean four year HbA_{1c} values. Finally, in children with high UA/UC diastolic blood pressure standard deviation score was significantly higher than in diabetics with normal UA/UC (1.14 (0.41) compared with 0.51 (0.24); $p < 0.01$).

We believe that raised urinary albumin excretion and diastolic blood pressure should be considered as risk factors for the development of clinical diabetic nephropathy in children.

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- 1 Gibb DM, Dunger D, Levin M, Shah V, Smith C, Barratt TM. Early markers of the renal complications of insulin dependent diabetes mellitus. *Arch Dis Child* 1989;64:984-91.
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Intravenous immunoglobulin in HIV infection

SIR,—Hague and colleagues have reported the use of intravenous immunoglobulin in eight children infected with human immunodeficiency virus (HIV).¹ They have been enthusiastic about its beneficial effects on both weight gain and frequency of infectious episodes. Furthermore they suggest that the intravenous immunoglobulin treatment resulted in significant saving of costs, despite the expense of the treatment, as a result of a decrease in the number of days the children spent in hospital.

We do not use routine intravenous immunoglobulin in children with symptomatic HIV infection and do not consider that their clinical course has been any worse than the children described by Hague *et al*. Five symptomatic children aged 22 months to 10 years infected vertically with HIV are attending the Hospital for Sick Children, Great Ormond Street, London. Failure to thrive in the first 18 months of life was prominent in the two children documented since birth, but resolved spontaneously with no specific treatment. In addition, numbers of infectious episodes and admissions to hospital were more frequent in the early months of life in all children. If we had begun intravenous immunoglobulin in these children at the onset of symptoms we might be claiming the apparent success of this treatment. Furthermore, based on the cost estimates of Hague *et al* we would have cost the National Health Service over £50 000.

There are major difficulties in the interpretation of uncontrolled studies of treatment efficacy, especially in a disease which is variable, and where the outcome measures may be related to age. HIV infection in children has

marked fluctuations in clinical manifestations and its natural history is not yet clear. The validity of comparing clinical measures such as weight gain and numbers of infectious episodes before and after an intervention is therefore highly questionable. Intervention is likely to begin at a time when a child is sicker than usual or has recently suffered an increase in symptoms and so by chance alone there are likely to be fewer recurring symptoms after the intervention. In addition the number of infections experienced by very young children (especially those living in deprived circumstances) is likely to decrease with increasing age.

Other reports of the use of intravenous gammaglobulin in children with symptomatic HIV infection have similarly been small, uncontrolled and retrospective.²⁻⁵ The lack of a controlled trial has resulted in a diversity of clinical practice concerning its use. The theoretical advantages are that it may decrease numbers of bacterial infections and provide passive immunity to children whose antibody response to antigenic stimuli may be poor. However, the not inconsiderable disadvantages include the risk of acquiring hepatitis C, the theoretical possibility of increasing HIV activation via antigenic stimulation, the psychological trauma and pain of giving intravenous infusions every three to four weeks to young infants, and finally the cost of treatment.

A recent survey of 32 centres in the USA including four AIDS clinical trial units found that of 95 severely ill children, 62% were receiving neither prophylactic antibiotics nor intravenous immunoglobulin and of 341 symptomatic, but less severely ill children, 84% received neither treatment. These results reflect the belief of many investigators that routine treatment with intravenous immunoglobulin should not be recommended without proof of efficacy.⁶ There are, of course, a small group of HIV infected children such as those with hypogammaglobulinaemia where this treatment may be beneficial.

There is, at present, a placebo control trial comparing intravenous immunoglobulin with intravenous albumin as placebo being conducted in the USA. Two hundred and thirty eight children from 25 centres in the USA have been recruited for the study and results are expected in the early 1990s.⁷ Until these are available no definite recommendations about the use of intravenous immunoglobulin in HIV infected children can be made, and its indiscriminate use should be discouraged.

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- 5 Gupta A, Novick B, Rubinstein A. Restoration of suppressor T-cell functions in children with AIDS following intravenous gamma globulin treatment. *Am J Dis Child* 1986;140:143-6.
- 6 Nicholas SW, Sondheimer DL, Willoughby AD, *et al.* Human immunodeficiency virus infection in childhood, adolescence, and pregnancy: a status report and national research agenda. *Pediatrics* 1989;83:293-308.
- 7 Riqua-Pérez JG (for the IVIG Clinical Trial Study Group, NIH Bethesda, Maryland, USA). Compliance with an intravenous immunoglobulin in HIV-infected children. Implications of AIDS for Mother and Child, Paris, Nov 1989. Abstract H3:177.

Drs Mok and Yap comment:

Dr Gibb and Dr Levin comment on our use of intravenous immunoglobulin in symptomatic HIV infected children,¹ and quote their experience based on five symptomatic HIV infected children. In the absence of details regarding age, symptoms, and laboratory criteria it is not clear if the five children in their group resemble the HIV infected children we describe in our paper, nor whether their children need any kind of treatment at all.

In addition, in two of their five children, failure to thrive was prominent in the first 18 months of life with spontaneous resolution, and infections were more frequent in the early months of life. In our paper, in only two of the eight children we studied was intravenous immunoglobulin treatment commenced earlier than 24 months, and in all children, strict criteria of at least two or more episodes of bacterial pneumonia, and a three month history of recurrent or chronic upper respiratory sepsis were used. Our children were clinically unwell, and we felt intervention in the form of treatment with intravenous immunoglobulin was justified, and not commenced prematurely.

Regarding the criticism that we used the number of infectious episodes and weight gain as criteria for evaluating intravenous immunoglobulin treatment, we felt that these were consistent and important features of the illness in HIV infected children and that these are key indices of morbidity to evaluate and to influence, if possible. Additionally, we quoted laboratory indices of HIV infection such as thrombocytopenia and the presence of HIV core antigen. There was suppression of the latter in the four children who were antigenaemic and it would be very unexpected for all the antigenaemic children that we studied (who were of different ages) to simultaneously lose their HIV core antigen.

The risk of acquiring hepatitis C infection from intravenous immunoglobulin is very small and only 43 patients have ever been reported in the world literature. The possibility of increasing HIV activation via antigenic stimulation is unlikely, and we have

demonstrated the opposite to occur—that is, a reduction in HIV antigen levels. We do agree that there may be psychological trauma and pain in administering intravenous immunoglobulin to young children. However, there is psychological trauma in repeated hospital admissions for illness, a factor that was reduced with intravenous immunoglobulin treatment.

Finally, we also agree that there have been few reports about the use of intravenous immunoglobulin in HIV infected children. However, the reduction in the incidence of infections and hospital admissions that we observed was of sufficient magnitude for us to recommend a change in clinical practice. The reasons for the difference in opinion put forward by Drs Gibb and Levin may be that although they describe their children as 'symptomatic', their HIV infected children may not in fact suffer as many infections as the HIV infected children we studied.

Breath hydrogen excretion in infants with colic

SIR,—McKenzie suggests that a shortened intestinal transit time with increased delivery of lactose to the colon might explain our finding of raised excretion of hydrogen in the breath of colicky infants.¹ Moore, Robb, and Davidson reported that there was no difference in the mean (SD) mouth to caecum transit time between colicky and non-colicky infants (63.9 (37.4) minutes compared with 58.1 (43.3) minutes, respectively).² Raised breath hydrogen excretion in colicky infants may be secondary to the behaviour but a faster transit of lactose in colicky infants does not explain our finding.

McKenzie also refers to the perception that babies with troublesome crying very often stop crying after hospital admission. This is not our experience. We documented the duration of crying and fussing in 46 healthy, 6 week old infants with unsettled behaviour who were admitted to a Tresillian Family Care Centre for a five day residential mothercraft programme. Thirty two (70%) of these infants still cried and fussed excessively (>3 hours/day) on the two days before discharge despite intensive mothercraft and paediatric and social worker support.

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1 McKenzie S. Breath hydrogen excretion in infants with colic. *Arch Dis Child* 1989;64:1208.

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ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the British Paediatric Association

Annotation	249 Sore throats <i>H Marcovitch</i>
	251 Editorial
Original articles	252 UKALL X—an effective treatment for stage III mediastinal non-Hodgkin's lymphoma <i>K Wheeler, J M Chessells</i>
	255 Haemophilus infection in cystic fibrosis <i>R J Rayner, E J Hiller, P Ispahani, et al</i>
	259 Serum IgA antibodies against <i>Pseudomonas aeruginosa</i> in cystic fibrosis <i>M M Brett, A T M Ghoneim, J M Littlewood</i>
	264 Rapid anticonvulsant monitoring in an epilepsy clinic <i>P N Houtman, S K Hall, A Green, et al</i>
	269 Pheochromocytoma—investigation and management of 10 cases <i>J E Deal, P S Sever, T M Barratt, et al</i>
	275 Hypertension after renal transplantation in patients treated with cyclosporin and azathioprine <i>N Gordjani, G Offner, P F Hoyer, et al</i>
	280 Symptoms in 298 infants under 6 months old, seen at home <i>A J Thornton, C J Morley, P H Hewson, et al</i>
	286 Home collection of urine specimens—boric acid bottles or Dipslides? <i>F E M Jewkes, D J McMaster, W A Napier, et al</i>
	290 Nocturnal enuresis in sickle cell haemoglobinopathies <i>D R J Readett, J S Morris, G R Serjeant</i>
	294 Persistent diarrhoea: clinical efficacy and nutrient absorption with a rice based diet <i>S K Roy, R Haider, M S Akbar, et al</i>
	298 Anorexia nervosa complicating inflammatory bowel disease <i>P Mallett, S Murch</i> Commentary <i>Lask</i>
	301 Langerhans cell histiocytosis: the case for conservative treatment <i>J McLelland, V Broadbent, E Yeomans, et al</i>
	304 Partial splenectomy in homozygous β thalassaemia <i>M de Montalembert, R Girot, Y Revillon, et al</i>
	308 Influence of inspiratory flow rate upon the effect of a Turbuhaler <i>S Pedersen, O R Hansen, G Fuglsang</i>
	311 High dose pancreatic enzymes in cystic fibrosis <i>P J Robinson, P D Sly</i>
	312 Dexamethasone treatment for congenital adrenal hyperplasia <i>M C Young, I A Hughes</i>
	314 Sialic acid storage disease <i>P D Cameron, V Dubowitz, G T N Besley, et al</i>
	315 Acute liver failure induced by carbamazepine <i>N Hadžić, B Portmann, E T Davies, et al</i>
	317 Contractural arachnodactyly with mitral regurgitation and iridodonesis <i>I C Huggon, J P Burke, J F Talbot</i>
Personal practice	320 Checking the health of school entrants <i>K Whitmore, M C O Bax</i>
Current topic	327 Antimicrobial treatment for urinary tract infections <i>K Verrier Jones</i>
	331 Neonatology—then and now <i>Walker</i>
	332 Letters to the editor
	338 Spring books

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ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the British Paediatric Association

Annotation

Sore throats

After four decades of treating sore throats with antibiotics, and on the assumption that medicine is a scientific discipline, it would be reasonable to expect that we know whether or not this method of treatment is logical.

General practitioners are unsure: in a two practice audit exercise, partners varied in their antibiotic prescribing rates for sore throat between 0% and 100%.¹ Paediatricians are no less uncertain. A study in a Connecticut paediatric practice showed that fever, lymphadenitis, pharyngeal injection, sore throat, headache, and abdominal pain all rapidly responded to penicillin or cefadroxil but there was no such prompt resolution with placebo,² provided the sore throat was caused by group A β haemolytic streptococci. So convinced was the editor of the *Journal of Pediatrics* that he appended the comment, 'This clinical study seems to provide the definitive answer to a frequently debated question'. Thankfully he used the word 'seems' because three years later he published, without editorial gloss, a multicentre double blind study which concluded that penicillin failed to provide significant symptomatic relief in sore throat caused by group A β haemolytic streptococci.³

One thing that is, however, clear is that penicillin is not of value in viral pharyngitis, which represents about 60% of all episodes of sore throat. Clinical manifestations are not such that it is easy to distinguish viral from bacterial disease, although experience must tell as the Connecticut paediatricians made a correct diagnosis in advance of culture results on 194 occasions out of 260, while the multicentre collaborators managed only 123 out of 271.

Even choosing an antibiotic is not totally straightforward as that organism, which has been sent to try paediatricians, *Mycoplasma hominis*, may be responsible for a small proportion of cases.⁴ Treating Epstein-Barr viral pharyngitis with ampicillin has led to litigation successful for the plaintiff.⁵

Symptomatic relief is not, of course, the major justification offered for antibiotic treatment. In the 1950s the knowledge that rheumatic fever and acute glomerulonephritis were provoked by group A β haemolytic streptococci infection led to the advice that these complications would be prevented by using penicillin to treat sore throats.⁶ In the United Kingdom in 1960, rheumatic fever was believed to follow about one in 300 streptococcal sore throats. In recent years, the risk of immunological problems with group A β haemolytic streptococci has fallen dramatically; the chance of developing rheumatic fever has been estimated at about one in 30 000 group A β haemolytic streptococci infections,⁷ and that of nephritis one in 13 000.⁸ Moreover the authors

could find no evidence that penicillin was any longer protective, although the numbers are surely too small for dogmatism. If these figures are correct they are a little too close in the risk-benefit equation to penicillin anaphylaxis at one in 10 000,⁹ and fatal reactions at one in 50 000.¹⁰ We can only wait to see if rheumatic fever makes enough of a comeback to tip the balance firmly on the side of benefit.¹¹

There are other reasons for treating group A β haemolytic streptococci with respect: septicaemia complicates a small number of cases and can be fatal. It may follow on from pharyngitis or, very occasionally, from scarlet fever—a toxic consequence of group A β haemolytic streptococci—now so uncommon as to be distinctly difficult for general practitioners to differentiate from the many viral infections which can cause sore throat, fever, and rash. Recently there have been reports from the United Kingdom,¹² United States,¹³ and Australia¹⁴ of a toxic shock like syndrome after group A streptococcal infection. Manifestations include acute renal failure, coagulopathy, and hepatic dysfunction. The virulence factors involved are diverse: in particular, the American cases being associated with pyrogenic exotoxin A while the B toxin was found in the British patients. After a decade or two of loudly declared injunctions from paediatricians that they use antibiotics too readily, who can blame general practitioners for sending infected children away with a prescription for paracetamol?

Should we then turn a double somersault and tell general practitioners they were right all the time? Penicillin just might be life saving; if group A β haemolytic streptococci cannot be reliably diagnosed clinically should all pharyngitis be treated to avoid the rare disaster? The answer depends on how much unnecessary treatment we countenance to protect the few who might not have recovered spontaneously.

Might consensus be easier to achieve if rapid diagnostic aids become available in the United Kingdom (and the NHS were prepared to meet their cost)? Numerous antigen detection test kits are available in the United States, so many indeed that one group of investigators has published a Consumers' Association style report and suggested a 'best buy'.¹⁵ In general the kits are highly specific but not quite so sensitive: the response of American physicians has been to start treatment earlier because of the backup of a positive test, but the problem of false negative results has led to no reduction in antibiotic prescribing for clinically suggestive cases.¹³ If, therefore, the aim is to make antibiotic treatment more precisely targeted these kits will need to be much more sensitive than their reported 60-70%.¹⁶

Asymptomatic carriers and family contacts pose a further

problem. It is often stated that infants rarely carry group A β haemolytic streptococci¹⁷; this is true for an unselected population but after an outbreak of streptococcal upper respiratory infection in an American day nursery, there was a carriage rate of 22% in children under 3.5 years (and 43% in older children).¹⁸ An effective way to eradicate carriage is to use a single dose of intramuscular penicillin (300–600 mg) and oral rifampicin (10 mg/kg every 12 hours for eight doses).¹⁹ A good case can be made out for treating chronic carriers who are in closed communities with high rates of streptococcal disease or who are hospital staff or long term inpatients. There is not yet any documented indication for treating carriers in the general population or within a family; indeed, asymptomatic carriage might protect from clinical disease and wholesale use of rifampicin might eventually destroy its effectiveness.

How should all this affect our teaching and practise? I instruct my juniors that when they become general practitioners they should treat streptococcal sore throats with penicillin even though we remain uncertain whether it makes patients feel better more quickly, because septic complications, though rare, might be avoided thereby. They should not conclude that by so doing they will prevent rheumatic fever or glomerulonephritis unless a 10 day course is prescribed,²⁰ and they should not expect too many patients to comply with such a regime. To avoid treating viral pharyngitis too frequently they should obtain throat swabs so that as the years go by they can test their own diagnostic accuracy.

They should consider treating the non-responder with erythromycin but not forget that there is an association between antibiotic prescribing for children and anxiolytic prescribing for their mothers.²¹ They must learn how to cope with the occasional patient who becomes seriously ill. This means, among other things, instructing parents—either verbally or through a handout—on the signs of sepsis, and how to recognise an ill child rather than simply advising them to return if they are worried. At the same time a simple explanation of fever control can be offered together with a prescription for paracetamol (or aspirin if over 12), especially for those at risk of febrile convulsions.

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Editorial

Writing economically

Short reports

A short report section is a feature of many scientific journals, but it must not be seen as a place for publishing original articles that have just failed to make the grade as a full article. As far as the *Archives* is concerned short reports are scrutinised with just as much care by the referees and editors, and they are assessed by the same yardstick of quality as longer articles. The only reason why a paper originally submitted as a full article might be accepted in the form of a short report is that we consider its contents are better presented in a shorter form—not because we have doubts about the paper's quality. We have deleted the title 'Short reports' from the front of the journal as a way of indicating that they have an equal status with other original articles.

There is a limit to the number of pages we can publish annually and by having short reports as well as standard length articles (normally 2000 words) we can give more authors the opportunity to have their work published. The reason for insisting on a limit to the number of words, illustrations, and references for a short report is that it makes the layout of the journal easier to plan by grouping together short articles of a similar length. If we allowed authors to extend those limits then there would be no short reports.

What material is best submitted in the form of a short report? Quite simply any original research that can be conveyed accurately in up to 900 words, two tables or figures, and up to six references. There is no doubt that some papers are improved when revised in a short report format, so presenting the reader with essentials that were previously hidden between the lines of unnecessary text. Against a background of competition for space, high quality original research has a priority over case reports but none the less a case report which has an important message or describes something new has a good chance of being published.

We all see from time to time patients with complex or unusual problems that generate a buzz in the hospital, often requiring multidisciplinary involvement in investigation and treatment. Although this might stimulate 'let's write it up' the resultant article will not usually be published unless there is an important message for readers that will advance knowledge of science or clinical medicine. Similarly a single case report of a rare condition or syndrome cannot have a high priority on the basis of its rarity alone. On the other hand a series of cases illustrating an established rare syndrome which is underdiagnosed (with important implications) might well be accepted because it carries a message. Also of potential interest is a series of cases illustrating the evolution of a syndrome phenotype with advancing age.

Strong evidence of a 'new' syndrome stands a high chance of being published as does an unusual association in an established syndrome. There must be a well reasoned argument that the association is probably based on a biological mechanism rather than coincidence. We appreciate that case reports involving descriptions of a phenotype often

demand more than two illustrations and in this instance exceptions to the rule will be made where appropriate.

Abstracts

The abstract or summary is the showcase of a scientific article. It is usually the first, and often the only, part which is read. Journals devoted to abstracting summaries are now common, and so one might think that the abstract would receive a high priority when creating a manuscript. We suspect that the opposite is the case. Although many authors do take great care to produce a readable and informative abstract, others seem to do a rushed job simultaneously with their letter of submission. It is quite common for us to receive a manuscript with no abstract at all.

Some are lucky enough to be gifted in their ability to summarise their ideas rapidly and communicate them economically—for example, the doctor on ward rounds who can describe a complex case in a few well chosen sentences. There is more time to marshal our thoughts when writing, and so summarising should be easier, but for most of us it rarely is. Newspaper journalists, in contrast, have no difficulty in summarising important research, reducing it to a short paragraph focusing on the sensational. Scientific writers have a more difficult task—they have to get their work across objectively.

There has to be a limit to the number of words allowed in the abstract. The scene should be set so that those unfamiliar with the subject can understand why the research was carried out; this should be followed by what was done, how it was done, what the results were, and the implications of those results. Some journals advocate structured abstracts with appropriate subheadings. Although this approach disciplines the writer and ensures that the key points are included, we feel that the stereotyped style is very dull to read. We wish to see readers attracted to articles outside their own field of interest, and in that respect the structured abstract might not be the appropriate showcase.

We are looking for the middle of the road approach—structured contents but not structured style. Perhaps the greatest challenge is summarising the results, particularly when the paper contains a mass of data. It is up to the author to tease out the data which are the thrust of the study. Other data may well be important but if too much is included the abstract will be difficult to grasp and the paper may not achieve the wide readership it deserves.

There is a parallel between writing an abstract for a paper and submitting an abstract for presentation at a scientific meeting. We suspect that good research is often excluded from presentation at meetings solely because the author paid insufficient attention to the presentation of the abstract. Our referees at least have the opportunity to read the whole manuscript before giving an opinion on its suitability for publication in the *Archives*. If the paper is published a well thought out abstract will help to ensure that the paper is widely read.

ORIGINAL ARTICLES

UKALL X—an effective treatment for stage III mediastinal non-Hodgkin's lymphoma

K Wheeler, J M Chessells

Abstract

Fifteen children with mediastinal non-Hodgkin's lymphoma were treated with MRC UKALL X, the current national protocol for acute lymphoblastic leukaemia. The treatment was well tolerated, and in a minimum follow up period of 46 months the event free survival of 93% was significantly better than that in a group of historical controls treated with intermittent chemotherapy regimens whose survival was only 57%. We conclude that intensive induction and consolidation treatment, with continued oral drugs, provides an effective approach to the management of mediastinal non-Hodgkin's lymphoma.

Mediastinal non-Hodgkin's lymphoma is an aggressive disease with a high risk of dissemination to the bone marrow and the central nervous system. Histological examination of the biopsy specimen of the mass or of the associated lymph nodes usually shows the features of lymphoblastic lymphoma, and immunological classification shows that nearly all these tumours have the features of immature T cells.¹ The relationship of T cell leukaemia to lymphoma is controversial, and there has been long standing debate about whether treatment should comprise an intermittent multiple drug regimen, or the type of continuous treatment that is used in acute lymphoblastic leukaemia.

We report here our experience of using the Medical Research Council United Kingdom acute lymphoblastic leukaemia (MRC UKALL)

X D protocol (one arm of the current national trial for the treatment of acute lymphoblastic leukaemia) in a group of children with mediastinal lymphoma, and compare their outcome with that of a group previously treated with intermittent regimens of several drugs.

Patients and methods

Fifteen consecutive children presenting from 1982 to 1985 were entered into the study (table). There were 11 boys and four girls and the median age at diagnosis was 6.5 years (range 1-15). The historical control group comprised 14 consecutive patients who presented between 1974 and 1981, of whom there were 10 boys and four girls with a median age of 6.5 years (range 2-13). There were no significant differences in age and sex distribution between the two groups.

The stage of the disease was established in all patients with a chest radiograph, bone marrow aspirate, and lumbar puncture, and the study patients also had an ultrasound examination of the abdomen. All the children had stage III disease according to the Murphy staging system—that is, extensive supradiaphragmatic disease without bone marrow or central nervous system disease.¹ The diagnosis (table) was determined by examination of biopsy specimens from lymph nodes in four children, from mediastinal masses in six, and by examination of pleural fluid in five. Immunological analysis of the material was carried out in 11 of the 15 cases, and in all the tumour was of T cell origin.

The historical group of patients had all

Clinical features of 15 patients treated with MRC UKALL X

Case No	Age (years)	Sex	Affected sites	Site of tissue diagnosis	Event free survival time (months from diagnosis)
1	13	Male	Mediastinum	Mediastinum	85
2	9.5	Male	Mediastinum, pleural fluid	Pleural fluid	83
3	11	Female	Mediastinum, supradiaphragmatic lymph nodes	Supradiaphragmatic lymph nodes	83
4	5	Female	Mediastinum	Mediastinum	82
5	6.5	Male	Mediastinum, pleural fluid, supradiaphragmatic lymph nodes	Pleural fluid	81
6	1	Male	Mediastinum, pleural fluid	Mediastinum	7
7	15	Male	Mediastinum	Mediastinum	64
8	2	Female	Mediastinum	Mediastinum	63
9	10	Female	Mediastinum, pleural fluid, supradiaphragmatic lymph nodes, kidney	Supradiaphragmatic lymph nodes	62
10	5	Male	Mediastinum	Mediastinum	56
11	6.5	Male	Supradiaphragmatic lymph nodes	Supradiaphragmatic lymph nodes	54
12	14	Male	Mediastinum, pleural fluid, kidney	Pleural fluid, kidney	53
13	5.5	Male	Mediastinum, pleural fluid	Pleural fluid	53
14	4	Male	Mediastinum, supradiaphragmatic lymph nodes	Supradiaphragmatic lymph nodes	49
15	5	Male	Mediastinum, pleural fluid	Pleural fluid	48

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received intermittent multiple drug regimens of repeated injections at intervals of three weeks; nine had been treated with the United Kingdom Childhood Cancer Study Group (UKCCSG) protocol, which has previously been reported.² The study patients received induction treatment with vincristine, daunorubicin, crisantaspase (L-asparaginase), prednisolone, and intrathecal methotrexate. Five received early intensification with a pilot schedule for MRC UKALL X and the rest received early and late intensification with several drugs, as previously described.³ Continuing treatment with prednisolone and vincristine every four weeks, daily 6-mercaptopurine, and weekly methotrexate, was given for two years from the time that remission was achieved. All patients received standard treatment to the central nervous system with cranial irradiation (18 Gy) and a course of intrathecal methotrexate injections.

All patients have now been followed up until June 1989, with a minimum follow up of two years without treatment. Difference in survival time between the two groups was calculated by the log rank method.⁴

Results

All 15 patients achieved remission. One child (the youngest in the series) relapsed with disease in the mediastinum seven months after diagnosis, and subsequently relapsed with disease in the central nervous system; he died one year after diagnosis. The others are all well and off treatment. The event free survival (figure) is 93% at four years, which is significantly better than that in the control group ($p=0.015$). Failures in the control group were due to one induction related death, two bone marrow relapses, two mediastinal relapses, and one relapse in the central nervous system.

Treatment was well tolerated. The toxicity of treatment was compared with that in children with lymphoblastic leukaemia receiving the same protocol.³ Only two of 15 children became febrile during induction, in contrast to 85% of those with leukaemia. The incidence of fever and gastrointestinal toxicity during intensifica-

tion was, however, similar. During the continuation of the treatment there were eight episodes of fever and neutropenia among the children with lymphoma, and there was one case each of varicella, *Pneumocystis carinii* pneumonitis, and candida pneumonia.

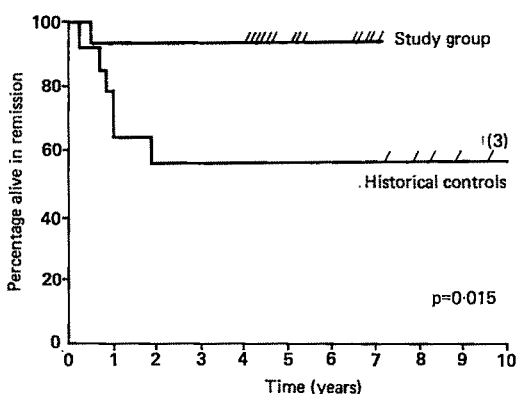
Discussion

These results show that a satisfactory outcome can be achieved in children with mediastinal (T cell) lymphoma using a regimen similar to that recommended for acute lymphoblastic leukaemia. We confined the report to children in whom the bone marrow was not affected, because of the problems of distinguishing acute lymphoblastic leukaemia from non-Hodgkin's lymphoma in children with marrow disease. Although this distinction may be an arbitrary one, we wanted to ensure that all the cases included would be unequivocally categorised as lymphoma.

The first reported improvements in survival in this disease were those of Wollner *et al* who used a complicated multiple drug regimen,⁵ the efficacy of which was subsequently confirmed by the American Children's Cancer Study Group.⁶ Workers at the St Jude Children's Hospital reported a 73% four year, event free survival for stage III and IV disease using a leukaemia protocol together with tenoposide and cytarabine.⁷ Our results confirm that a satisfactory response to treatment can be obtained without recourse to long term rotating drug schedules. The benefits of a comparatively simple and familiar approach are obvious, although it should be noted that this form of treatment is not suitable for the other types of childhood non-Hodgkin's lymphoma, which are largely tumours of B cell origin.

Despite the intensity of induction and consolidation, the short term toxicity of treatment was acceptable; as expected there were less infective problems during induction than in children with acute lymphoblastic leukaemia, because in no child was the bone marrow affected initially. Our results were achieved without local irradiation, which was given to only one child as emergency treatment for mediastinal obstruction. It seems that if chemotherapy is sufficiently intensive, local irradiation is not necessary to achieve either remission or long term survival. Treatment to the central nervous system is essential because of the tendency of lymphoma to recur in the central nervous system, and our patients received cranial irradiation and intrathecal methotrexate. The morbidity of cranial irradiation is well described, and it remains to be established whether intrathecal and systemic chemotherapy will provide an effective and less toxic substitute.

The results of this pilot study suggest that the UKALL X protocol is an effective treatment for mediastinal non-Hodgkin's lymphoma without bone marrow involvement. The protocol has since been adopted by the UKCCSG for national use so that confirmation of its efficacy and assessment of results in patients with stage IV disease should ultimately be available.



Event free survival in study patients and historical controls. The number of children who have been followed up for longer than 10 years is shown in parentheses.

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Haemophilus infection in cystic fibrosis

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Abstract

Twenty seven patients with cystic fibrosis under the age of 12 years and 27 matched patients with asthma were followed up in a prospective study for one year. The isolation rate of non-capsulated strains of *Haemophilus influenzae* from cough swabs and sputum specimens taken at routine clinic visits every two months was significantly greater in cystic fibrosis than in asthma. *Haemophilus parainfluenzae* was equally common in both groups. During exacerbations the isolation rate of *H influenzae* in cystic fibrosis was significantly greater than at other times, whereas in asthma there was no significant difference.

The distribution of biotypes of *H influenzae* and *H parainfluenzae* was similar in the two groups. In cystic fibrosis, biotype I was associated with exacerbations. Biotypes V was more common than in previous studies, but was not associated with exacerbations.

In recent years, non-capsulated *Haemophilus influenzae* has become well established as an important human pathogen in both adults and children.¹⁻³ Non-capsulated strains of *H influenzae* and *Haemophilus parainfluenzae* colonise the lower respiratory tracts of patients with cystic fibrosis but may also be found in the upper respiratory tracts of normal children.⁴ Some cystic fibrosis centres adopt a policy of treating all patients from whom *Haemophilus* spp have been isolated, irrespective of the clinical state of the patient.⁵ *H influenzae* and *H parainfluenzae* have been subdivided by Kilian on the basis of three biochemical characteristics (ornithine decarboxylation, indole production, and urea hydrolysis) into several biotypes.⁶ Biotypes I of *H influenzae*, which is known to be associated with acute otitis media in normal children,³ was isolated significantly more often from patients with cystic fibrosis than from healthy controls.⁷ To assess the importance of *H influenzae* and *H parainfluenzae* in cystic fibrosis and the value of biotyping, we conducted a prospective study to determine the rates of isolation and the distribution of biotypes from the respiratory tracts of children with cystic fibrosis. Children with asthma were used as controls because they were likely to have increased respiratory secretions without significant bacterial infection.

12 years who lived within easy reach of the hospital were invited to take part in the study. The next suitable patient seen in the asthma clinic, matched for age and sex, was invited to act as a control. Consent was obtained from the parents and the study was approved by the hospital ethical committee. Patients were seen routinely every two months and weekly during acute respiratory exacerbations. At each visit weight and height were recorded and where possible lung function tests were performed using a Wright peak flow meter and an electronic spirometer. The best of three readings was recorded in each case and was expressed as a percentage of the predicted value for height. Pulse, respiratory rate, and physical signs were scored by one of us (RJR) and the parents were asked to score symptoms of cough, wheeze, and breathlessness on a scale of 0 (none) to 4 (severe). The two scores were added together for analysis. At the start of the study, peak flow records and symptom charts were kept for two weeks to assess baseline variability during a period when the child was well. The parents contacted the hospital at any time when the child was unwell with increased cough, wheezing, or breathlessness and peak flow records and symptom scores were recorded until symptoms had resolved.

During acute exacerbations, patients with cystic fibrosis received a two week course of amoxycillin. Those aged less than 1 year, between 1 and 8 years, and over 8 years received 125, 250, and 500 mg of amoxycillin respectively every eight hours. If *Staphylococcus aureus* had been isolated recently amoxycillin was combined with flucloxacillin or occasionally erythromycin was prescribed. If the child was allergic to amoxycillin or the *Haemophilus* spp was resistant to ampicillin, co-trimoxazole was prescribed. Patients who were chronically infected with *Pseudomonas aeruginosa* were treated with intravenous antibiotics when necessary. In contrast, asthma patients did not receive antimicrobial treatment but inhaled therapy was adjusted and, if necessary, courses of oral steroids were prescribed for acute exacerbations. Cough swabs were repeated after one and two weeks of treatment in both groups.

Cough swabs were taken by a standard method either by the outpatient sister or by one of us (RJR). The swab was held at the back of the child's throat and he or she was asked to cough. In the case of young children it was sometimes necessary to induce a gag reflex. The swabs were placed in Stuart's transport medium and labelled sequentially with a number so that the microbiologists were unaware of the identity

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Patients and methods

PATIENTS

All patients with cystic fibrosis under the age of

of the patient. In addition, whenever possible a sputum specimen was sent for culture in the usual way. A throat swab was placed in viral transport medium and sent for viral culture at the start of each exacerbation.

METHODS

Each cough swab was broken off into a bijoux bottle containing 0.5 ml of 2% N-acetylcysteine. It was shaken briefly in a Whirlmixer (Fisons) to distribute the swab contents. Using a Pasteur pipette a drop was placed on to plates containing heated blood agar, chocolate agar, crystal violet agar, and a selective chocolate agar (containing cefsulodin 8 mg/l, which inhibited *Pseudomonas* spp but allowed *Haemophilus* spp to grow). The drops were spread in the usual way and the plates were incubated at 37°C in 5% carbon dioxide for 18 hours. Isolates were identified as belonging to *Haemophilus* spp by typical colonial morphology, microscopic appearance, and growth requirement for 'X' and 'V' factors. All isolates of *H. influenzae* were designated non-capsulated if they failed to agglutinate with type specific *H. influenzae* type b (Public Health Laboratory Service) and polyvalent (Difco, types a-f) antisera or if they autoagglutinated. Other organisms were identified by standard methods.⁸ The biotypes of isolates were determined using the RapID/NH system (Merck Diagnostics). All isolates of *H. influenzae* and *H. parainfluenzae* were tested for β lactamase production by the technique of Escamilla⁹ and additional disc diffusion sensitivity tests were carried out by Stokes' method¹⁰ with discs containing ampicillin 2 and 10 μ g. Discs containing sulphamethoxazole 50 μ g, trimethoprim 2.5 μ g, chloramphenicol 10 μ g, and cefotaxime 30 μ g were used to test isolates which were resistant to ampicillin.

Data were analysed by χ^2 tests, one way analysis of variance, and paired *t* tests using SPSSX programmes.

Results

There were 27 patients in each group with a predominance of boys in both groups (cystic fibrosis, *n*=18 and asthma, *n*=17). The median ages in the cystic fibrosis and asthma groups were 7.5 and 7.1 years respectively. The median Shwachman score¹¹ in the group with cystic fibrosis was 82 (range 43-94), and the median Crispin-Norman x ray score¹² was 6 (range 2-20). Five patients with cystic fibrosis were chronically infected with *P. aeruginosa*. In the asthma group, 19 patients were taking inhaled steroids and six were taking inhaled sodium cromoglycate. Twenty one patients in each group were able to perform reliable respiratory function tests.

There were 80 exacerbations in the group with cystic fibrosis and 34 in the group with asthma. Exacerbations were associated with a fall in mean peak expiratory flow rate (PEFR) and forced expiratory volume in one second (FEV₁) in both groups (*p*<0.05) and a rise in mean clinical score. There was an improvement in mean PEFR and FEV₁ by the second week of antibiotic treatment (*p*<0.05) in the group with cystic fibrosis (figure).

Four hundred and ninety cough swabs or sputum specimens (cystic fibrosis, *n*=303 and asthma, *n*=187) were examined between January and December 1988. *H. influenzae* was isolated on at least one occasion from 21 patients with cystic fibrosis and eight with asthma (*p*<0.001), and on three or more occasions from six cystic fibrosis patients but no asthmatics. All strains of *H. influenzae* isolated were non-capsulated. *H. parainfluenzae* was isolated on at least one occasion from six patients with cystic fibrosis and two with asthma. Table 1 shows the isolation rates of *H. influenzae*, *H. parainfluenzae*, and other pathogens from specimens obtained at routine clinic visits, in the month preceding an acute exacerbation, during exacerbation, and after starting treatment (after exacerbation). At routine clinic visits, before and during exacer-

Graphs to show the mean (SE) values for peak expiratory flow rate (PEFR), forced expiratory volume in one second (FEV₁), and clinical score in the two groups according to type of visit.

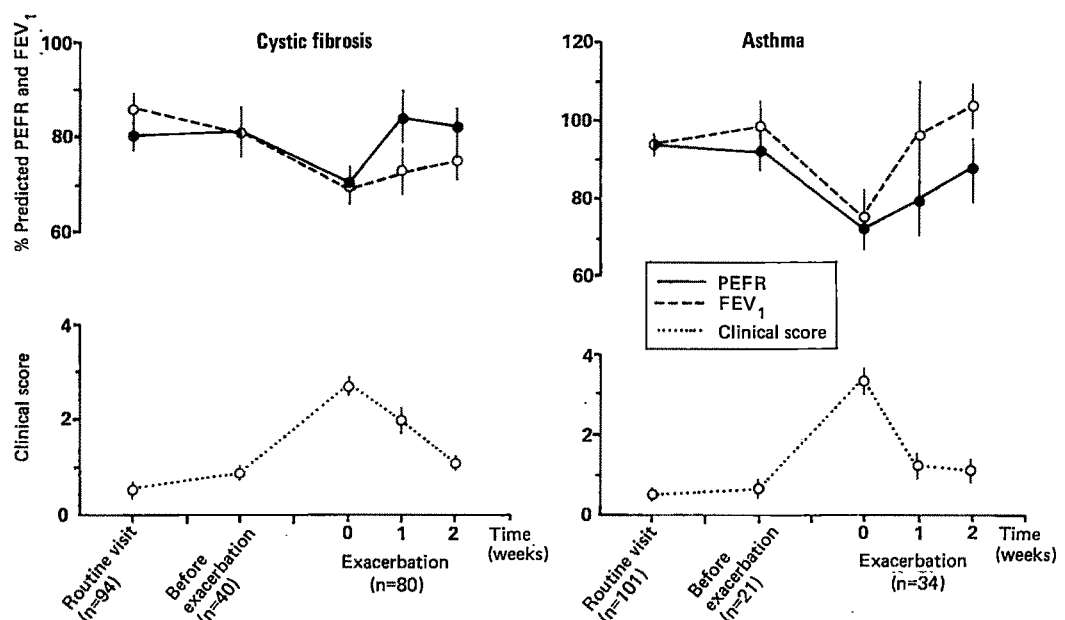


Table 1 Number (%) of isolates of *H influenzae* and *H parainfluenzae* and other pathogens in the two groups according to type of visit

Type of visit	Cystic fibrosis				Asthma			
	No of specimens	<i>H influenzae</i>	<i>H parainfluenzae</i>	Other pathogens only	No of specimens	<i>H influenzae</i>	<i>H parainfluenzae</i>	Other pathogens only
Routine	94	24 (25.5)	3 (3.2)	12 (12.7)	101	8 (7.9)	3 (3)	0
Before exacerbation	40	15 (37.5)	2 (5)	5 (12.5)	21	2 (9.5)	1 (4.8)	1 (4.8)
Exacerbation	80	31 (38.8)	2 (2.5)	14 (17.5)	34	1 (2.9)	2 (5.9)	0
After exacerbation	89	7 (7.9)	0	14 (15.7)	31	3 (9.7)	1 (3.1)	1 (3.1)
Total	303	77 (25.4)	7 (2.3)	45 (14.8)	187	14 (7.5)	7 (3.7)	2 (1.0)

bations, *H influenzae* was isolated more frequently from patients with cystic fibrosis than from asthma patients ($p < 0.01$). After antibiotic treatment, the rate of isolation of *H influenzae* from patients with cystic fibrosis was similar to the isolation rate from asthma patients. The isolation rate of *H influenzae* in the cystic fibrosis group increased from 25.6% at routine visits to 38.8% during exacerbations ($p < 0.05$). In contrast, the isolation rate of *H parainfluenzae* remained low at all visits and was equal in the two groups. Of those specimens from which other pathogens only were isolated, *P aeruginosa*, *S aureus*, and group A haemolytic streptococci accounted for 30, 14, and one isolates respectively in cystic fibrosis, whereas in asthma the two isolates were both group A haemolytic streptococci.

Viral cultures performed during exacerbations yielded coxsackievirus, rhinovirus, and Herpes simplex virus in three patients with cystic fibrosis and cytomegalovirus in one patient with asthma.

Seventy nine strains of *H influenzae* and 14 strains of *H parainfluenzae* were biotyped. All but one strain of *H parainfluenzae* were biotype III. The distribution of biotypes of *H influenzae* was not significantly different in the two groups (table 2). Biotype V was more common than biotype I in both groups and occurred with equal frequency at routine clinic visits and during exacerbations. Biotype I was isolated more frequently around the time of an exacerbation (11 isolates) than at other times (four isolates). Patients with cystic fibrosis frequently harboured a particular biotype for several months, but some showed a change in biotype before an exacerbation.

Nine isolates of *H influenzae* (cystic fibrosis, $n=8$ and asthma, $n=1$) were ampicillin resistant

and all except one produced β lactamase. Five of eight β lactamase producing strains were biotype V. Two strains of *H parainfluenzae* were ampicillin resistant.

In patients with cystic fibrosis from whom *H influenzae* only was isolated during an exacerbation, a 14 day course of oral amoxycillin was always associated with a clinical response. Eradication of *H influenzae* was achieved on 15 out of 22 (70%) occasions. It is our practice to treat all patients with cystic fibrosis from whom *S aureus* is isolated, irrespective of symptoms.

Discussion

The role of non-capsulated *H influenzae* in adults with lower respiratory tract infections is now widely recognised, but in children its role remains unresolved. This is because it is frequently isolated from the upper respiratory tract in normal children and it is known that invasive infections in children are almost always due to capsulated type b strains of *H influenzae*. Nevertheless, non-capsulated strains are undisputed pathogens of otitis media and sinusitis in children,³ and in a large study of community acquired pneumonia in children, more than half the strains of *H influenzae* producing pneumonia were non-capsulated.¹³

The results of this study suggest that *H influenzae* is a significant pathogen in children with cystic fibrosis. *H influenzae* was more frequently isolated from the lower respiratory tract in cystic fibrosis than in asthma. Furthermore, a rise in the isolation rate of *H influenzae* preceded the development of acute exacerbations in the patients with cystic fibrosis and clinical improvement coincided with a reduction in the isolation rate after antimicrobial treatment (table 1). In this age group *H influenzae* may be a more frequent pathogen than *P aeruginosa*. *S aureus* has been less frequently isolated in recent years because it is usually eradicated by elective antimicrobial treatment. Placebo controlled double blind trials would be needed to establish whether elective treatment of *H influenzae* isolates in young cystic fibrosis patients reduces the frequency of acute exacerbations.

In adults with chronic bronchitis the symptoms produced by infection with *H influenzae* and *H parainfluenzae* are indistinguishable,¹⁴ but no similar study has been carried out in children. This study has not found any difference between the groups in the isolation rate of *H parainfluenzae* or in the distribution of its

Table 2 Distribution of biotypes of *H influenzae* from patients with cystic fibrosis and asthma

Biotype	No (%) of strains	
	Cystic fibrosis	Asthma
I	15 (24.2)	4 (23.5)
II	10 (16.1)	2 (11.8)
III	4 (6.4)	4 (23.5)
IV	2 (3.2)	0
V	21 (34.0)	5 (29.4)
VI	3 (4.8)	0
VII	3 (4.8)	0
Non-typable	4 (6.4)	2 (11.8)
Total	62 (100)	17 (100)

biotypes. As *H parainfluenzae* was much less frequently isolated than *H influenzae*, a larger study would be needed to rule out the possibility that it may be associated with exacerbations in cystic fibrosis.

In this study the biotype distribution of *H influenzae* isolates from children with cystic fibrosis and asthma was similar. Previous studies have suggested that biotype I may be more common and biotype II less common in cystic fibrosis than in normal children.⁷ The value of biotyping strains of *H influenzae* in determining pathogenicity lies mainly in the detection of biotype I.³ As in this study less than one third of isolates during exacerbations were biotype I, biotyping may be of limited value in clinical practice. Other methods of typing non-capsulated *H influenzae*, for example based on outer membrane proteins, may be more useful.¹ Temporal changes in the biotype distribution of *H influenzae* have been described. Therefore, the finding that biotype V was more common than in previous studies may merely reflect the passage of time, geographical differences, or selection of ampicillin resistant strains.¹⁵ Even when strains of *H influenzae* are apparently sensitive to ampicillin, only 70% of courses of amoxycillin eradicate *H influenzae* from the lower respiratory tract, as previously reported by Pressler *et al.*⁵ This may be due to inadequate penetration of the antibiotic into the sputum. The use of very high doses of amoxycillin has been advocated in adults with bronchiectasis¹⁶ and may be effective in children.

The isolation rate of viruses in this study was low, but nasopharyngeal cultures taken on the first day of illness and paired blood samples for viral serology might have yielded more positive results.¹⁷ Secondary bacterial infection may occur in cystic fibrosis as a result of damage to the respiratory epithelium during viral infection. *H influenzae* may colonise the upper respiratory tract initially and then migrate to cause lower respiratory tract infections in the damaged bronchi of cystic fibrosis patients. *H influenzae* is capable of producing histamine *in vitro*,¹⁸ which might contribute to inflammation and airflow obstruction in cystic fibrosis. This study has shown that antibiotic treatment for *H influenzae* was associated with clinical improve-

ment and with the eradication of the organism in most cases. Therefore, we feel that antimicrobial treatment should be considered seriously in patients with cystic fibrosis from whom non-capsulated *H influenzae* is isolated, particularly during exacerbations.

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Serum IgA antibodies against *Pseudomonas aeruginosa* in cystic fibrosis

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Abstract

Serum IgA antibodies to *Pseudomonas aeruginosa* cell surface antigens were estimated by ELISA. Titres in patients with and without cystic fibrosis and with no pseudomonal infection were low (<105 to <261). Titres in patients with cystic fibrosis who were chronically infected with *P aeruginosa* were very high (1200-163 000), and patients who grew the organism intermittently had intermediate titres. Longitudinal studies suggested increasing tissue invasion or involvement of the lower respiratory tract, or both, with increasing time of infection and identified patients with a good prognosis after the onset of pseudomonal infection. Detection of an increased serum IgA titre can give an earlier indication than measurement of the serum IgG titre of the presence of *P aeruginosa* in the respiratory tract in a proportion of patients. IgA measurement seems to be better than IgG measurement at predicting the reappearance of *P aeruginosa* after apparent eradication of early infection. These results suggest that this assay may be a valuable additional indicator of the presence of *P aeruginosa* at the beginning of infection, and of the reappearance of the organism after treatment in the early stages of infection.

Despite the widespread use of effective anti-pseudomonal antibiotics, pulmonary infection with *Pseudomonas aeruginosa* remains a major cause of morbidity and mortality in patients with cystic fibrosis.¹ A full understanding of the immunological processes involved in the initial stages of infection of the respiratory tract should assist in successfully combating such infection. The pronounced systemic IgG response to pseudomonal infection has been well documented.²⁻⁴ Because the bronchial and pulmonary mucosa are the primary sites of infection, IgA antibodies might be expected to have an important role in combating infection, but this is not well understood. The sequence of events in response to infection of a mucosal site should first be production of IgA and secretory IgA (sIgA), which should agglutinate the organisms and so prevent them from growing and from attaching to the host mucosa. When the IgA response is inadequate, IgG antibodies will be produced.⁵ It is possible that patients with cystic fibrosis have a quantitative defect in their IgA response that renders them susceptible to infection. In addition, IgA has been reported to be the major humoral immune response in the upper respiratory tract of dogs while IgG

predominates in the lower respiratory tract,⁵ so comparison of the IgA and IgG responses may give an indication of the depth of infection. We therefore decided to measure serum IgA antibodies to *P aeruginosa* in different stages of pulmonary infection, and to compare this with antipseudomonal IgG antibodies in patients' serum.

Patients and methods

Serum samples were obtained from 139 patients with cystic fibrosis who attended the paediatric and adult clinics at our hospital. *P aeruginosa* had never been isolated from 33 patients. Their age range was 1-16 years, mean (SE) 7.3 (1.04). *P aeruginosa* was isolated on one or more occasions from 57 patients, but they had no recognisable chest illness attributable to that organism. Their ages ranged from 1-26 years, mean 7.26 (1.71). Forty nine patients had recognisable chest illness that was attributable to *P aeruginosa*, which had been isolated continuously for at least six months. Their ages ranged from 10-27 years, mean 15.6 (1.18).

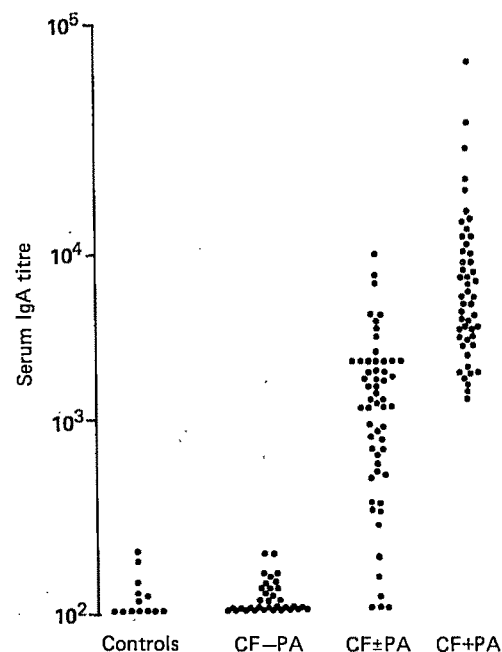


Figure 1 Serum IgA antibody titre to *P aeruginosa*. IgA antibody titre is the sum of individual titres to *P aeruginosa* strains with serotypes 1, 3, 6, 9, 10, 11, and a strain that could not be serotyped. Controls: paediatric patients with no history of *P aeruginosa* infection; CF-PA: patients with cystic fibrosis from whom *P aeruginosa* had never been isolated; CF±PA: patients with cystic fibrosis from whom the organism had been isolated at least once; CF+PA: patients with cystic fibrosis from whom *P aeruginosa* had been isolated continuously for at least six months.

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Overall clinical state was assessed by the Shwachman score.⁶ Declining scores indicate a worsening condition. Films from chest radiography were assessed by the Chrispin-Norman x ray score.⁷ An increasing score indicates increasing abnormality.

The controls comprised 13 patients who attended a paediatric clinic for other reasons. The mean age was 9.2 (1.4) years, varying from 8 months to 15 years. None had any evidence of lung disease or *P aeruginosa* infection.

Serum samples from all the subjects were stored at -20°C until immediately before analysis.

Free serum IgA antibodies to *P aeruginosa* cell surface antigens were measured by enzyme linked immunoabsorbent assay (ELISA) as previously described.⁸ Seven strains of *P aeruginosa* with serotypes 1, 3, 6, 9, 10, 11, and a strain that could not be serotyped were used.⁹ The serum was diluted 1:200 or 1:2000.

Kendall's rank correlation test¹⁰ and the Mann-Whitney U test¹¹ were used for statistical analysis.

Results

Free serum IgA titres against *P aeruginosa* in controls and patients with cystic fibrosis are shown in fig 1. The titres of 13 control patients ranged from <105 to <261, mean (SE) 127(13). The titres of 34 patients with cystic fibrosis, from whom *P aeruginosa* was never isolated during the next three years, ranged from <105 to <216, mean 127 (6.0).

Forty nine patients with cystic fibrosis who had chronic *P aeruginosa* all had very high serum IgA titres (between 1200 and 16 300), which were significantly greater than control titres ($p < 0.001$).

There was a wide range of titres in patients with cystic fibrosis with intermittent *P aeruginosa*: 51/57 patients had titres that were greater than the control range, between 275 and 6650. There were two patients in whom IgA titres remained within the control range throughout the study period, despite intermittent isolations of *P aeruginosa* and increases in IgG titre. No difference in the rate of change of lung function or chest radiography could be detected between these two patients and patients who had increased IgA and IgG titres. Four patients with intermittent *P aeruginosa* isolations had titres between 105 and 235, which were within the control range. These four patients are considered in more detail in table 1. *P aeruginosa*

was isolated one to three times during a short period from each of these patients. Both IgA and IgG titres were within the control range in serum samples taken at varying times before and after these isolates. Serum IgA and IgG concentrations were also within the normal range throughout the study periods in all four patients.

P aeruginosa was isolated for the first time from 26 patients with cystic fibrosis during the study period. An increase in serum IgA titre, to greater than the control range, was detected up to 24 months before *P aeruginosa* was first isolated in all 26 patients (fig 2). This appears to be a similar pattern to that previously reported for the IgG titre,¹² but if the IgA and IgG titres are compared, some differences begin to emerge. The IgA titre increased four to 20 months before an increase in IgG titre was detected in eight patients. This was followed by intermittent *P aeruginosa* isolations. In contrast, the IgG titre increased nine and 11 months before the IgA titre increased in two patients. In 16 patients, IgA and IgG titres were both greater than control values in the first available serum sample, one to 24 months before the first isolation of *P aeruginosa*. In the absence of anti-pseudomonal intravenous treatment there were further increases in the IgA titre, both before and after the beginning of *P aeruginosa* isolations. Longitudinal studies of three representative patients are shown in fig 3.

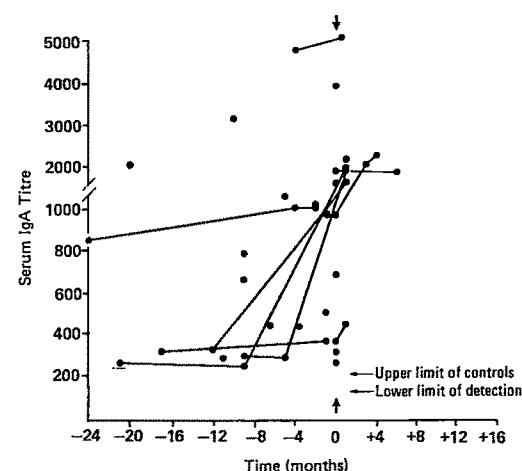


Figure 2 Serum IgA antibody titre to *P aeruginosa* in 26 patients with cystic fibrosis before and after the first isolation from the respiratory tract. The arrows indicate the time of the beginning of intermittent isolations of *P aeruginosa*. The upper limit of controls is the statistical limit of 99.9% plus 10% interassay error.

Table 1 Titre of IgA and IgG antibodies to *P aeruginosa* in patients with cystic fibrosis before and after transient isolation from the respiratory tract

Age (years)	Sex	No of positive isolations/No of samples tested	Before isolation			After isolation			Months without <i>P aeruginosa</i>
			IgA	IgG	Time sample taken (months)	IgA	IgG	Time sample taken (months)	
4	F	1/32	<210	<160 <170	16.5 3	<114 <150	<190 <150	7 17	24
1	M	1/26	<105	<140	1	<105 <105 <115	<140 <140 <140	0 6 7	23
6	M	3/17	<105	<240	10.5	<105	<160	16	7
8	M	2/16	<180	<140	20	<105	<170	3	12

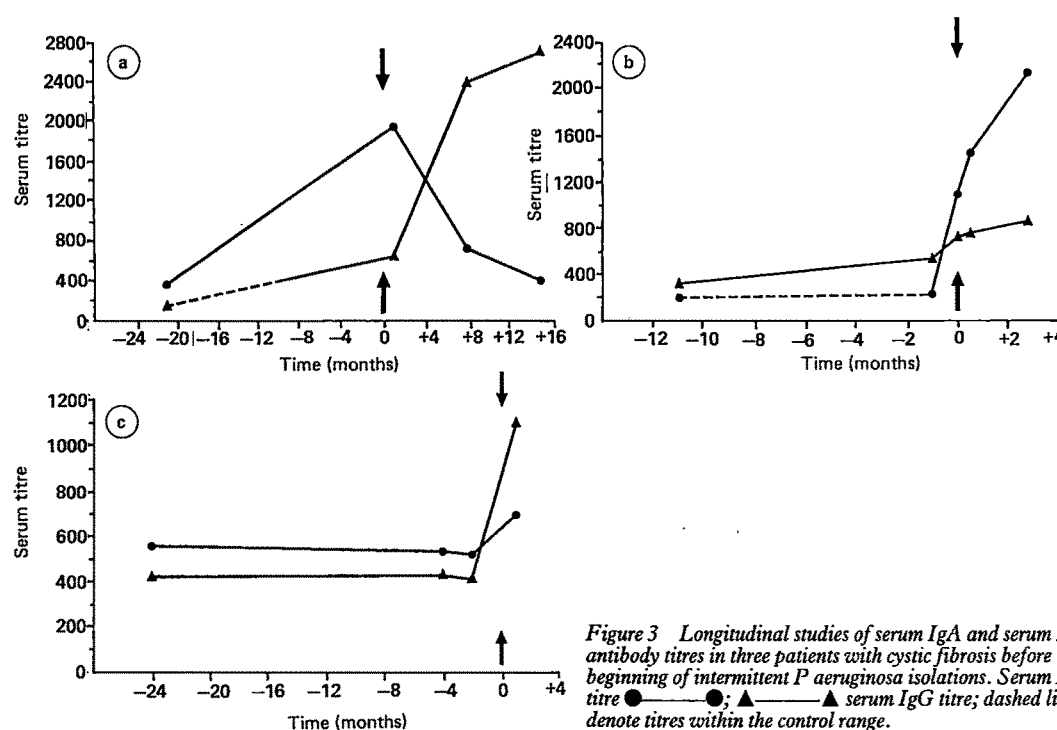


Figure 3 Longitudinal studies of serum IgA and serum IgG antibody titres in three patients with cystic fibrosis before the beginning of intermittent *P. aeruginosa* isolations. Serum IgA titre ●—●; serum IgG titre ▲—▲; dashed lines denote titres within the control range.

A follow up study of six patients from whom the organism was not isolated and the serum IgG titre returned to control concentrations after intravenous treatment showed that in five patients the organism reappeared (five to 37 months after intravenous treatment). In five patients an increase in IgA titre to greater than the control range, followed by further increases in titre, preceded the organism's reappearance (table 2). The IgG titre increased in only one patient before the reappearance of *P. aeruginosa*. It did not increase until after intermittent isolations had begun in the other four patients.

A comparison of IgA and IgG titres in the different groups of patients is shown in table 3.

Patients with no known pseudomonal infection had ratios of IgA:IgG titres between 0.35 and 1.65. Patients with intermittent *P. aeruginosa* had a significantly higher ratio than chronically infected patients ($p < 0.001$), although there was a wide range of values in the two groups and some overlap between them. Longitudinal studies of individual patients in both groups showed that in the absence of intravenous treatment, the ratio gradually decreased with increasing time of infection. There was no correlation between the ratio of IgA:IgG titres and Shwachman score or Chrispin-Norman score in the groups of patients who grew *P. aeruginosa* intermittently or chronically.

Table 2 Serum IgA and IgG titres in patients with cystic fibrosis before the recurrence of infection

Case No	Age (years) and sex	Before treatment*			After treatment			
		Time sample taken (months)	IgA	IgG	Time sample taken (months)	IgA	IgG	<i>P. aeruginosa</i> reisolated (months)†
1	5F	9.5	790	485	0	(220)	(140)	>31
					22	250	(140)	
					26	1630	(150)	
2	15M	1	370	340	0	320	(190)	33
					22	370	(140)	
					29	370	(140)	
3	4F	15	ND	475	11	290	(190)	37
					15	300	(144)	
					23	350	(230)	
					37	580	(170)	
					42	ND	690	
4	11F	19.5	240	450	0	1250	(170)	23
					9	1540	375	
					26	ND	420	
5	23F	0	320	430	0	410	(230)	5
					4	460	(270)	
					9	490	535	
6	25F	2	1100	580	13	690	(214)	14
					23	1100	390	
					26	2600	590	
					31.5	10 000	4700	

Figures in parentheses indicate titres within the control ranges. ND=not done.

*Treatment was two weeks of an intravenous aminoglycoside (for example, tobramycin, amikacin) and a ureidopenicillin (for example, azlocillin, piperacillin).

†The time after treatment when *P. aeruginosa* was reisolated from the patient.

Table 3 Ratio of serum IgA titre to serum IgG titre in patients with cystic fibrosis

	IgA:IgG		Shwachman score	Chrispin-Norman score	IgA titre	IgG titre
	Mean (2 SD)	Range				
<i>P. aeruginosa</i> not present (n=33)	0.72 (0.53)	0.35-1.65	75-100	0-6	<105-<200	<140-<240
Intermittent <i>P. aeruginosa</i> (n=38)	2.2 (0.19)	0.69-5.05	65-90	2-11	176-2800	306-1050
n=1(a)	6.0, 9.7*		100	2	3500, 6640	370, 950
Chronic <i>P. aeruginosa</i> (n=35)	1.05 (0.15)	0.07-3.55	45-85	9-24	1200-16 300	1200-20 500
n=1(b)	9.7, 14.2*		95	3	1600, 1980	<140, <166

*Denotes significance of $p < 0.001$. Each patient is represented by one value except (a) was seven readings two years apart and (b) was two readings three years apart.

There were, however, two patients (one with intermittent and one with more than five years of chronic *P. aeruginosa*) who stood out as being different. They both had a significantly higher ratio of IgA:IgG titres than the other patients in the corresponding group ($p < 0.001$), which was maintained over a period of several years. This was due to a very pronounced IgA response and a very low IgG response. Both patients had much higher Shwachman scores and lower Chrispin-Norman scores than the other patients in the same group.

Discussion

All patients with cystic fibrosis with chronic pseudomonal infection had a very pronounced IgA response. Patients with intermittent *P. aeruginosa* also had titres greater than the control range, with the exception of six patients. Two of these six patients had no detectable increase in serum IgA titre throughout periods of 12-22 months of repeated *P. aeruginosa* isolations and increased IgG titres, which are indicative of infection.^{12, 13} There was no difference in clinical variables between these two patients and patients who had increased IgA titres. Consistent changes in clinical variables, however, are detectable only in patients with chronic pseudomonal infection,² so these two patients may need to be studied for a longer time before any conclusions can be drawn on the effect of a lack of specific serum IgA antibodies on their prognosis. Furthermore, a lack of IgA antibodies in serum should be interpreted with caution in the absence of data on concentrations in sputum: a dissociation between local and systemic concentrations of precipitins against *P. aeruginosa* and *Staphylococcus aureus* has been reported for some antigens in a small number of patients with chronic infection.¹⁴

In contrast, four patients had no detectable increase in both IgA and IgG titres during periods of up to 17 months before and after one to three isolations of *P. aeruginosa*. Serum concentrations of IgA and IgG remained within the normal range throughout the study period. It is unlikely that antibodies to *P. aeruginosa* were present in serum but not detected: the outer membrane proteins of *P. aeruginosa* are highly conserved,¹⁵ and the serotypes of isolates from these patients were included in the assay. The absence of a systemic IgG response implies the absence of tissue invasion and infection,^{12, 13} and the lack of a detectable systemic IgA response suggests that either local pulmonary antibody synthesis was adequate or that isolates were transient and not present in either suffi-

cient numbers or for sufficient time to induce systemic IgA. It should be emphasised that this was not a common finding: the vast majority of our patients from whom *P. aeruginosa* was isolated are infected.

Among all patients with an IgA titre greater than the control range there was no correlation between IgA titre and the Chrispin-Norman chest x ray score, even in patients with chronic pseudomonal infection, where pulmonary changes are more pronounced and predominantly caused by *P. aeruginosa*. IgA production is an initial immune response to the presence of an infective agent in the pulmonary cavity, and one of its main functions is to prevent adhesion of organisms to pulmonary mucosa.⁵ IgA production is, therefore, unlikely to bear any relation to the amount of tissue fibrosis and endobronchial inflammation which contribute to the chest x ray score. Indeed, increased IgA production could occur with no detectable change in the chest radiograph if it prevents bacterial adherence to pulmonary mucosa and hence tissue damage. If the IgA response is not sufficient to prevent bacterial growth and adhesion then IgG production is induced, which we have shown to correlate with changes in chest x ray score.²

The results presented here show that the vast majority (90%) of patients with cystic fibrosis produce specific IgA antibodies before the organism is present in sufficient numbers to be isolated from the respiratory tract (10^4 - 10^5 colony forming units/ml in our laboratory) but this does not prevent pseudomonal infection becoming established and eventually overwhelming. It is possible that although the serum titre is increased, the sputum concentration is not increased or is insufficient to cope with the bacterial load. A defect in the assembly of sIgA has been reported,¹⁶ which would render it more susceptible to cleavage by proteases produced by *P. aeruginosa*. Another possibility is that, although the IgA concentration in the lungs is adequate, there are defects in non-specific components, such as ciliary movement or phagocytosis, so that removal of organisms from the respiratory tract could be suboptimal.

The presence of serum IgA antibodies, which have been shown to be specific for *P. aeruginosa*,⁸ at higher concentrations than normal would seem to indicate the presence of the organisms in the respiratory tract. It could be argued that increased serum IgA antibodies in the absence of serum IgG antibodies signifies harmless colonisation, rather than tissue invasion and infection. What is perhaps of greatest importance to the patient is treatment at a stage

when the course of infection can be radically altered.

We have shown previously that treatment at an early stage of infection apparently eradicated pseudomonal infection (as judged by bacteriology and serum IgG titres) in six of 16 patients.¹² After intervals of five to 32 months, *P. aeruginosa* again began to be isolated from five of these six patients. It appears that IgA measurement may be better than IgG measurement at predicting the recurrence of pseudomonal infection: an increase in IgA titres was detected in all five patients before the organism reappeared, whereas an increase in IgG titre was only detected in one patient. This was an unexpected finding; the cause and its significance are unclear, but should be clarified.

Because both IgA and IgG are involved in the immune response to *P. aeruginosa* we considered the association between them. The ratio of IgA:IgG titres decreased in individual patients with increasing time of infection, so patients with intermittent *P. aeruginosa* had a significantly higher ratio of IgA:IgG titres than patients with chronic *P. aeruginosa*. There was some overlap between the two groups, presumably due to the arbitrary division between them. There were two patients (one with intermittent and one with chronic *P. aeruginosa*) who stood out as being totally anomalous. They both had ratios that were significantly higher than other patients in the same group, maintained over study periods of two to three years. These two patients both showed a lack of clinical deterioration: their clinical state and chest radiograph were dramatically better than those of the other patients in the corresponding group. Both these patients had a very pronounced IgA response and an IgG response that was very low or absent. A high ratio of IgA:IgG could be caused in two ways, both of which suggest a less damaging infection. A high ratio could be indicative of an IgA response which is sufficient to prevent tissue invasion and so there is no stimulus to induce IgG production. Alternatively, it is possible that, as IgA antibodies predominate in the upper airways while IgG antibodies predominate in the lower respiratory tract,⁵ a high ratio could indicate an infection predominantly in the upper airways while a low ratio suggests infection deeper in the lungs.

In conclusion, the serum IgA response to *P. aeruginosa* seems to follow a similar pattern to that of serum IgG antibodies: titres were very low in patients with no history of pseudomonal infection, high in patients with intermittent

P. aeruginosa, and very high in patients with chronic *P. aeruginosa*. Measurement of IgA titres has confirmed that *P. aeruginosa* isolates were transient and non-pathogenic in a small proportion of patients. Comparison of the IgA and IgG titres identifies those patients with a very good prognosis after the onset of pseudomonal infection. These results suggest that IgA measurement could improve still further patient management in two situations. First, by predicting the reappearance of *P. aeruginosa* after apparent eradication and secondly, in some patients, by giving an even earlier indication than IgG measurement of the presence of the organism in the respiratory tract in the very earliest stages of infection.

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Rapid anticonvulsant monitoring in an epilepsy clinic

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Abstract

The relevance of providing a rapid anticonvulsant monitoring service was assessed over a five year period at a paediatric epilepsy outpatient clinic. Altogether 481 drug assays were performed on 144 patients when considered clinically indicated. Drugs most frequently assayed were carbamazepine and sodium valproate, singly or in combination; 90% of assays performed for phenytoin were from patients who were also taking another anticonvulsant. There were only six assays for ethosuximide and 10 for phenobarbitone.

Physician's choice of drug dosage was recorded on a questionnaire before and after each assay result was known. Comprehensive patient details were analysed by a paediatric clinical pharmacologist, whose decision as to total daily anticonvulsant dosage was affected by knowledge of the drug concentration significantly less often than that of the clinicians for all the more commonly assayed drugs.

There were a large number of drug assays that had no discernable clinical application. A more discriminating use of assays may both improve patient management and reduce considerably the number of anticonvulsant assays required.

Monitoring of anticonvulsant drugs is considered an essential part of the management of epilepsy.^{1,2} Confidence in the concept that attending to the plasma concentrations of these drugs is the main factor in treating most patients has lessened, however, and this is true in paediatric as well as adult practice.³⁻⁵

Anticonvulsant monitoring is considered relevant to several areas of management. Firstly it is useful in those patients receiving drugs such as phenytoin or multiple treatment regimens in whom dose related toxicity or poor seizure control necessitates dosage adjustment. Secondly, it can be used as an aid in the assessment of toxicity particularly in those with mental or physical handicap, and possibly in young children. Thirdly, it is useful in the presence of systemic disease when drug handling may be affected unpredictably; finally it can be used in checking compliance.^{3,6}

There is usually a delay of several hours or days between the taking of a specimen and a result being available to the clinician. The use of a monitoring service in which the result is immediately available clearly has potential advantages, as any relevant changes in drug treatment can be discussed and instituted without need for further consultation, direct or

indirect. Apart from these practical advantages it has been difficult to show objectively a major effect on patient management.^{7,8}

This study documents the usefulness of such a service in a paediatric epilepsy clinic, but also assesses the effects on drug usage.

Patients and methods

The study was conducted over a five year period from 1982 in the specialist epilepsy outpatient clinics at the Children's Hospital, Birmingham. The patients were seen by one of three consultants experienced in the management of paediatric epilepsy.

Those patients in whom drug assays were considered to be clinically indicated had capillary blood samples taken immediately after an initial interview. In each case, the clinician filled a specifically designed request form on which were not only relevant patient details, drug doses, and the time the last dose was given, but also the proposed course of management in the absence of knowledge of drug concentration.

Plasma drug concentrations of carbamazepine, sodium valproate, phenytoin, ethosuximide, and phenobarbitone were measured using the enzyme multiplied immunoassay technique.⁹ The results were available within 20 minutes.

Each patient was seen again and a continuing treatment regimen established using knowledge of the drug concentrations. At this point the clinician completed the form describing the action taken with knowledge of drug concentration.

At the end of the study period, each completed assay request form was transcribed by one investigator (PNH) onto a further form giving patient details as in the clinical request form but excluding the patient's name. In the great majority of cases, however, the patients' clinical records were also investigated so that a more detailed appraisal of disease activity, including a three tier arbitrary scale of severity and any recent trends, could be documented. These forms contained at least as much, and in most cases considerably more, information than would be provided on an assay request form. The other investigator, a paediatric clinical pharmacologist (GWR) examined these forms and in the absence of knowledge of drug concentration documented his proposed drug management strategy. The drug concentration was then added to the form and his opinion given in the light of the drug assay result. The 'investigating pharmacologist' thus emulated

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the clinician in being initially 'blind' to the drug concentration. An attempt at documenting follow up information was made through the perusal of the clinical notes but this assessment was subjective.

Results

PATIENT AND ASSAY STATISTICS

A total of 349 blood samples was collected from 144 patients (79 boys, 65 girls) over a five year period. Sixty five patients were tested at the clinic on more than one occasion during the study. Ages ranged from 1 to 20 years and the median age was 11 years. No patient had significant hepatic or renal disease.

One hundred and two samples (29%) were from patients who had major motor seizures alone; 88 (25%) were from those with temporal lobe epilepsy; 33 (10%) with petit mal epilepsy, and 32 (9%) with partial seizures. Twenty one samples (6%) were taken on those with myoclonic jerks and 18 (5%) on those with febrile convulsions. A further 55 (16%) had a mixed epilepsy picture. The above classification into types of epilepsy is not necessarily standardised, and takes into account the nomenclature used by the consultants responsible for the cases.

A total of 481 assays was performed. Figure 1 shows the distribution of samples with respect to drugs assayed. Thus 238 (68%) samples were assayed for carbamazepine and 180 (52%) for sodium valproate. About half of these samples were assayed for two anticonvulsants. A total of

229 samples (66%) were assayed for only one drug, 74 (21%) for carbamazepine and sodium valproate, 35 (10%) for other combinations of two drugs, and 11 (3%) for three drugs (carbamazepine, sodium valproate, and phenytoin in all cases). Of samples processed for phenytoin assay, 42 patients (90%) were also taking another anticonvulsant. In contrast, in the small number of ethosuximide assays performed, no patient was on another anticonvulsant.

DISTRIBUTION OF PLASMA CONCENTRATIONS

The distributions of plasma concentrations for carbamazepine, sodium valproate, and phenytoin are shown in fig 2. For the other drugs the numbers were small; in the case of ethosuximide the maximum plasma concentration was 62 mg/l (440 μ mol/l) and for phenobarbitone it was 28 mg/l (120 μ mol/l).

COMPLIANCE

Referring to patient notes, it was possible to identify 18 incidents in which compliance was considered to be a significant factor in failure of drug management. Of these, only five assays could be said to have contributed to the assessment of non-compliance by being less than that expected by the clinician. In six patients, however, there was some degree of communication problem involving drug management to the extent that the patient did not receive the drug regimen considered applicable. There was also a high proportion of cases (at least 10%) in which parents themselves would adjust the anticonvulsant dose between clinic appointments, depending on clinical features.

TOXICITY

For carbamazepine there were eight documented cases of significant side effects. Three of these were transient involving lethargy on starting the drug. The others involved visual disturbances and in one case there was a possible related change in behaviour. The carbamazepine concentration was 12–16 mg/l (50–68 μ mol/l) in all cases of supposed toxicity. For sodium valproate there was one case of nausea and three cases of sparse or curly hair growth. There was only one case of documented phenytoin toxicity, that of ataxia (phenytoin concentration 22.3 mg/l (88 μ mol/l)), and no cases of ethosuximide or phenobarbitone toxicity.

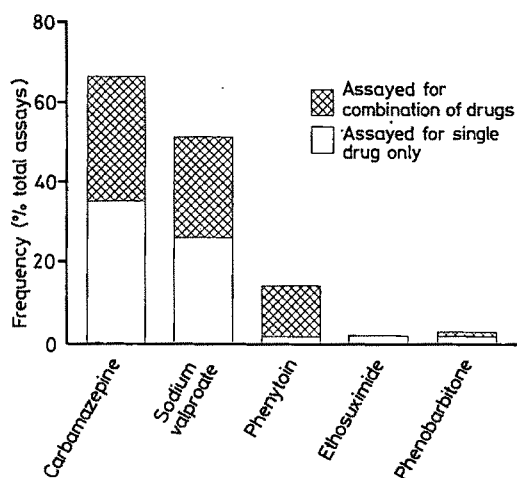


Figure 1 Number of assays performed for each drug as a percentage of total assays.

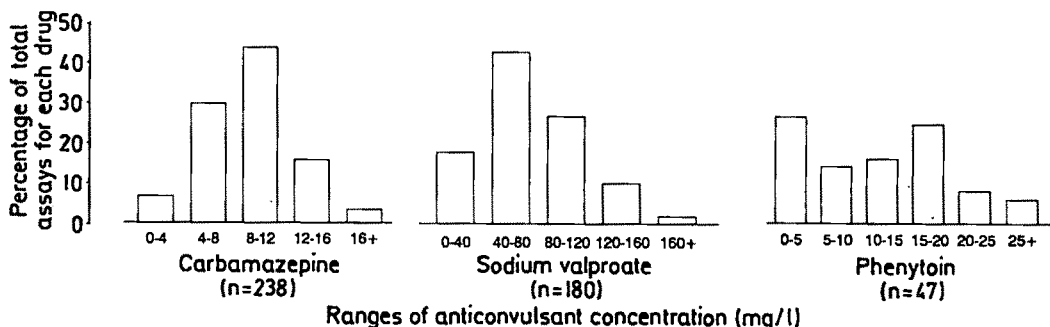


Figure 2 Distribution of assays in relation to concentration ranges for carbamazepine, sodium valproate, and phenytoin. To convert mg/l to μ mol/l: carbamazepine, $\times 4.2$; sodium valproate, $\times 6.9$; and phenytoin, $\times 4.0$.

DRUG DOSE—CONCENTRATION ASSOCIATIONS

There were positive linear correlations between the weight related dose and drug concentration for carbamazepine and sodium valproate ($r=0.46$ and $r=0.36$ respectively; $p<0.001$). For phenytoin a positive association was shown when subdividing into plots of individual patients who had more than two drug assays, as exemplified in fig 3.

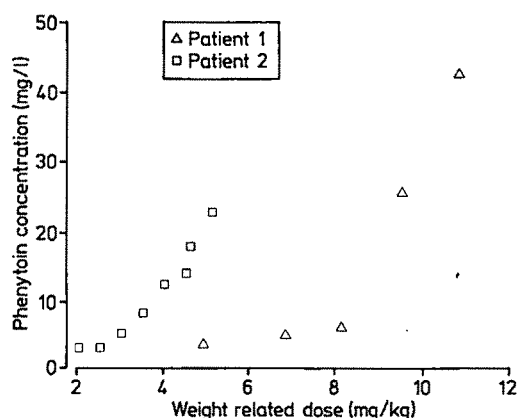


Figure 3 Association between weight related dose and drug concentration for phenytoin in two patients. To convert mg/l to $\mu\text{mol/l}$: phenytoin, $\times 4.0$.

EFFECT OF DRUG CONCENTRATION ON PATIENT MANAGEMENT

Action of clinician

Table 1 shows the action taken by the clinicians in terms of changes made to total daily anticonvulsant dose as a percentage of the total number of assays for each drug. For carbamazepine a proposed decision by the clinician to change the total daily dose before knowledge of drug concentration was made in 19% of cases, and this proportion was slightly more with knowledge of the concentration. For sodium valproate and phenytoin the initial figure was approximately 30% of cases, and again there was an increase in the number of total daily dose changes made after knowledge of the drug concentration. The low numbers for ethosuximide and phenobarbitone prevent any meaningful analysis of the data.

Table 1 also shows the proportion of cases in which there was any change in decision making by the clinician from that before to that after knowledge of the drug concentration; this includes those cases where an initial decision to change dosage was cancelled or reversed on knowledge of the level.

Figure 4 shows the percentage of drug doses changed for carbamazepine, sodium valproate, and phenytoin in relation to the concentration range in which the result fell.

Table 1 Clinician: changes of treatment and decision

Drug	Change of treatment (% of total)		Change of decision (% of total)
	Before knowledge	After knowledge	
Carbamazepine (n=238)	19	23	14
Sodium valproate (n=180)	29	36	22
Phenytoin (n=47)	32	51	34
Ethosuximide (n=6)	(17)	(17)	(0)
Phenobarbitone (n=10)	(10)	(20)	(10)

Figures in parentheses denote small sample numbers.

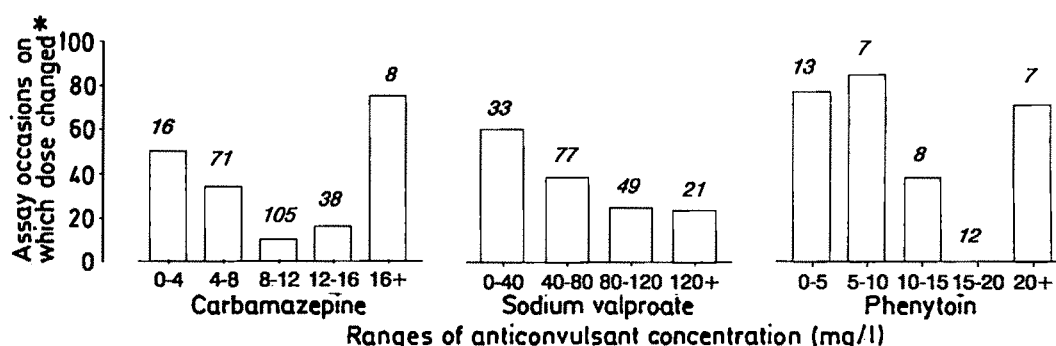


Figure 4 Occasions on which dose changed by clinician in relation to concentration ranges for carbamazepine, sodium valproate, and phenytoin. The numbers are the total within the concentration range; *% of total within range. To convert mg/l to $\mu\text{mol/l}$: carbamazepine, $\times 4.2$; sodium valproate, $\times 6.9$; and phenytoin, $\times 4.0$.

Table 2 Pharmacologist: changes of treatment and decision

Drug	Change of treatment (% of total)		Change of decision (% of total)
	Before knowledge	After knowledge	
Carbamazepine (n=238)	57	57	8
Sodium valproate (n=180)	49	49	12
Phenytoin (n=47)	70	80	23
Ethosuximide (n=6)	(17)	(33)	(17)
Phenobarbitone (n=10)	(40)	(70)	(30)

Figures in parentheses denote small sample numbers.

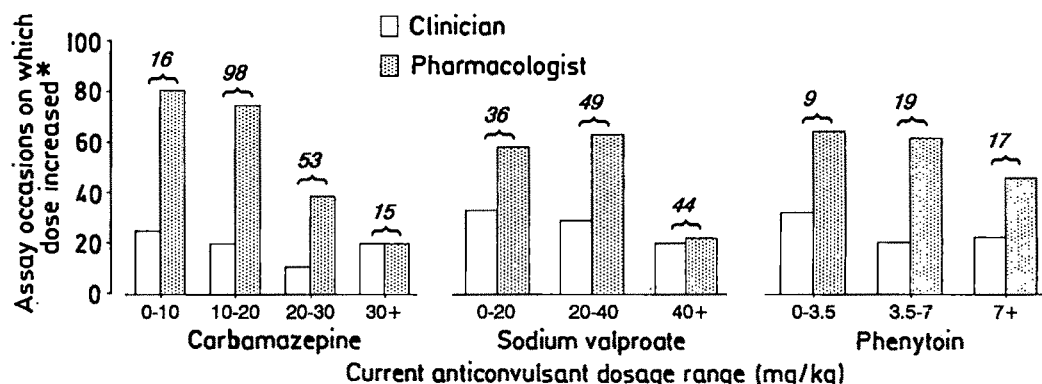


Figure 5 Occasions on which dose increased in relation to current dosage range for carbamazepine, sodium valproate, and phenytoin. The numbers are the total within dosage range; *% of total within range.

Actions of pharmacologist compared with clinician Table 2 shows the actions proposed by the paediatric pharmacologist, and these results relate to table 1 for the clinician.

There were considerable differences between the actions of the clinicians and those of the paediatric pharmacologist. In approximately half of all assays the proposed course of action differed between the two, both before and after knowledge of drug concentration. Figure 5 compares the actions of clinician and pharmacologist with respect to weight related total daily dose before drug concentration was known. In this figure only those patients whose investigation forms had led to a designation of moderately severe or severe epilepsy are included, as patients with mild epilepsy might be considered to be well enough controlled even if receiving low doses of anticonvulsants. The pharmacologist was considerably more likely to increase the dose throughout the range of doses but particularly so at the lower end of the dosage range.

Discussion

Knowledge of anticonvulsant plasma concentration affected the clinicians' treatment plans in only a small proportion of cases. Although these findings alone may suggest that therapeutic drug monitoring was simply a wasted exercise in the vast majority of cases, the only direct measure of the usefulness of such assays would be to assess clinical effectiveness in some way. Such a global study would be unlikely to succeed because, even with a relatively large sample size as in this study, there are too many variables of morbidity in the population of children with epilepsy as a whole, and with regard to time in an individual patient, for such a study to be objective.¹⁰ Instead this study provides information about some of the factors involved in monitoring of anticonvulsant concentration, and is of value to the clinician in evaluating the need for an assay result in an individual case.

The changes in decision making by the clinicians were not evenly spread between the anticonvulsant drugs. We have shown that children exhibit saturation kinetics well within the clinical range of plasma concentrations for phenytoin (fig 3).^{11 12} This would be a contribu-

tory factor in accounting for the large number of samples where the plasma concentration was barely detectable and also the significant number well above the recognised therapeutic range of plasma concentrations. This unpredictability of the plasma concentration would also explain the considerably increased number of changes of decision after knowledge of the concentration made by the clinician for phenytoin over other anticonvulsants. In contrast, for carbamazepine there were few changes of decision and as might be expected, the plasma concentrations of the assays formed a fairly symmetrical distribution around the recognised therapeutic range indicating a high level of predictability. It has recently been reported in adult practice that changes to treatment dosage are made throughout the range of drug concentrations (MJ Brodie. Abstract presented at 4th biannual British/Danish/Dutch epilepsy congress, Amsterdam, September 1988) but, in this study and for carbamazepine at least, there was a strong tendency for the clinician not to change dosage when the drug concentration was in the middle of the therapeutic range (fig 4).

For sodium valproate there appears to be some confidence in a lower limit for therapeutic range but there is no evidence from these data that there is a well defined upper limit for desirable drug concentration. This supports the current view that plasma concentrations of sodium valproate are a poor predictor of efficacy.^{13 14} The relevance of plasma monitoring for valproate is further put into question when it is considered that although we found that there was a highly significant correlation between the weight related dose and plasma concentration, the wide scatter of results meant that only just over 10% of this association could be accounted for by a linear correlation.

Comparison of the clinicians' and the paediatric pharmacologist's approach showed considerable differences. Tables 1 and 2 show that the pharmacologist was likely to change drug dosage significantly more often than clinicians for all the more commonly assayed drugs. But in terms of changes in decision making in the light of knowledge of drug concentration, the pharmacologist made even fewer decision changes than the clinician. In looking for an explanation for these differences there were obviously factors which could not be controlled

for, particularly the fact that the clinicians actually saw the patients and their families so that decisions were based on relationships between doctor and patient and these could not be transcribed to a written form. Further scrutiny of the results, however, suggests that much of this difference might be accounted for by the pharmacologist tending to increase dosage proportionally more than the clinicians at the lower end of the weight related dosage range. Only those patients having repeated fits are included in this assessment, as those patients free of fits must be considered to be well controlled. Figure 5 confirms that the pharmacologist was considerably more likely to increase the dose throughout the range of dosages but particularly so at the lower dosages. In other words the pharmacologist seemed more aware of the concept of achieving a more appropriate weight related dose than the clinician.

As most assays were performed when the clinician had little apparent intention of changing the drug dosage regimen even without knowledge of drug concentration, it might be supposed that these assays were being done to assess toxicity or compliance. It is perhaps surprising that although there were many phenytoin concentrations well above the recognised plasma therapeutic range, there was only one case of documented toxicity for this drug.¹⁵ Toxicity therefore must have had little effect on the proportion of decision changes. Although compliance is accepted to be a major factor in problems of management, this study showed that in only a small number of cases was the discovery or the assessment of the non-compliance significantly attributable to the assays.

The epidemiological data in this study can have only indirect relevance to the population of children with epilepsy as a whole. For example, in assessing toxicity, the data are of value only for dose related events, and so give no information about the incidence of such idiosyncratic reactions as carbamazepine induced rashes. Similarly the data on the type of epilepsy are more reflective of the apparent need for anticonvulsant monitoring than the distribution of epilepsies in childhood. Compared with carbamazepine and sodium valproate, only a small minority of phenytoin assay samples were from patients not taking another anticonvulsant, so that phenytoin appears to be a 'second line' drug in paediatric practice.

A rapid drug monitoring service is expensive, and in this case the cost was at least double that of a conventional drug monitoring service. The cost is in part proportional to the number of assays performed at each clinic session. The advantage of rapid monitoring to this type of study, however, is that it provides the oppor-

tunity for the clinician to document a judgment on drug treatment strategy before and after knowledge of the drug concentration without allowing the passage of time to reduce the power of the comparability between the two decisions. A rapid assay service must also be directly advantageous to patient management. In the area of compliance this study has shown that patients do not always receive the intended continuing dosage regimen even with the rapid assay service. Taking into account the practical advantages of communicating directly with the patient, the efficiency of the service cannot be measured merely by comparing basic costs. As in no case did the clinician make any change in decision after knowing the drug concentration for ethosuximide, however, the cost of this drug assay may not be justified.

In conclusion, this study has shown that a large proportion of drug measurements have no discernable clinical application. Differences between the pharmacological characteristics of individual anticonvulsant drugs have been shown but the clinician often does not use the data provided appropriately. A more discriminating use of data from assays may both improve patient management and cut down considerably on the number of anticonvulsant assays required.

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Phaeochromocytoma—investigation and management of 10 cases

J E Deal, P S Sever, T M Barratt, M J Dillon

Abstract

Since 1960 we have diagnosed phaeochromocytoma (paraganglioma) in 10 children. The cases include a 15 year old girl who over a three year period presented with multiple paragangliomata and an associated malignant carotid body tumour. All children were hypertensive, eight of 10 presenting with severe headaches. Diagnosis was based on finding a raised urinary vanillylmandelic acid excretion and plasma noradrenaline concentration. In addition six of eight children were hypercalcaemic with raised plasma calcitonin concentrations; plasma parathyroid hormone concentrations were high in two of seven and four out of eight children had raised plasma renin activities on presentation. No child, however, was found to have a multiple endocrine neoplasia syndrome. Despite the introduction of newer techniques for the detection of catecholamine producing tumours we found that selective arteriography and venous catecholamine sampling were superior for tumour localisation compared with ultrasound scanning, computed tomography, and meta-iodo-benzyl-guanidine (MIBG) scanning.

Phaeochromocytoma is a rare but treatable cause of hypertension in childhood.¹ At the Hospital for Sick Children, Great Ormond Street, London, which is a tertiary referral centre for childhood hypertension, 1.3% of cases referred over a 10 year period, for investigation of high blood pressure, were found to have a phaeochromocytoma (table 1). In children there is a higher incidence (32%) of multiple tumours and an increased occurrence of the multiple endocrine neoplasia syndromes when compared with that reported in adults.¹ The incidence of malignancy is 2.4%, compared with a malignancy rate of 10% in adults.²

Table 1 Diagnoses of 454 cases of hypertension admitted to the renal unit at the Hospital for Sick Children, 1975-85, including six of the children reported here

Diagnosis	No (%) of children
Coarse renal scarring:	
Reflux nephropathy	84 (19)
Obstructive uropathy	72 (16)
Glomerular disease	123 (27)
Renovascular disease	38 (8)
Haemolytic uraemic syndrome	32 (7)
Polycystic kidney disease	22 (5)
Idiopathic (essential)	18 (4)
Renal dysplasia	13 (3)
Wilms' tumour	9 (2)
Coarctation	7 (<2)
Phaeochromocytoma	6 (<2)
Renal vein thrombosis	4 (1)
Miscellaneous	26 (6)

A system for the classification of tumours of the autonomic nervous system was proposed by Glenner and Grimley in 1974 and is now widely accepted.³ Under this classification a tumour arising from the adrenal medulla is termed a phaeochromocytoma and chromaffin tumours arising outside the adrenals of paraganglionic origin are termed paragangliomata. Paragangliomata are more commonly found at extra-adrenal sites in children than in adults and can occur anywhere in the autonomic nervous system. Tumours of the carotid body, in association with phaeochromocytoma, have been frequently reported in adults,^{4 5} but there is only one report in the literature of an affected child, that of a 12 year old boy.¹ We report here 10 cases of paragangliomata, including one child with multiple lesions and a malignant carotid body tumour, that have been seen at the Hospital for Sick Children since 1960.

Patients

REVIEW OF CASES

Clinical details of all 10 children are summarised in table 2; the cases are tabulated in chronological order of presentation. They ranged in age from 3.5 months to 16 years, mean age 10.3 years. Only three children were less than 10 years old at presentation.

The commonest presentation in the present series was severe headaches; varying in duration from 11 days to 2.5 years. The youngest child (case 3) presented with episodes of diarrhoea and sweating and two generalised fits, presumed to be due to her hypertension, at the age of 3 months. All children were hypertensive; in eight children it was sustained and in only two was the blood pressure labile. One girl (case 10) was diagnosed fortuitously: although asymptomatic she was found to be hypertensive at an outpatient clinic visit where she was being followed up for a stage IV Wilms' tumour that had been diagnosed and treated seven years previously by chemotherapy, radiotherapy, and a right nephrectomy.

Another girl (case 7) who presented with headaches, pallor, and tachycardia, was initially found to have two para-aortic paragangliomata. After surgical removal of these she presented over the subsequent three years with two further extra-adrenal tumours, bilateral intra-adrenal tumours, and a malignant carotid body tumour, which were all surgically removed.

Two children had a positive family history: one (case 10) had an uncle who had been diagnosed some years before her presentation and the other (case 9) had a 17 year old sister

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Table 2 Clinical details of the 10 children with phaeochromocytoma in chronological order of presentation

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age at presentation (years)	13.3	12.6	0.3	7.5	10.1	10.4
Sex	Male	Female	Female	Female	Male	Female
Presenting symptoms	Headaches, convulsion	Headaches, pallor, abdominal pain	Diarrhoea, sweating	Headaches	Headaches, convulsion	Headaches, sweating
Investigations:						
Urinary vanillylmandelic acid	↑	↑	↑	↑	↑	↑
Plasma noradrenaline (pg/ml)*	—	—	1371	5130	18 345	27 700
Plasma renin activity	—	—	N	N	↑	↑
Calcitonin	—	—	↑	↑	↑	↑
Parathyroid hormone	—	—	—	N	—	N
Plasma calcium (mmol/l)	—	—	2.7	2.64	2.75	2.64
Preoperative treatment	Phentolamine	Phenoxybenzamine, propranolol	Phenoxybenzamine, propranolol	Phenoxybenzamine, propranolol	Phenoxybenzamine	Labetalol, phenoxybenzamine, propranolol
Site and size of tumour (cm)	Right adrenal 5×4	Right adrenal 7×6	Left adrenal 0.3×0.3	Right adrenal 5×3	Left adrenal 5×5	Right adrenal 3×2.5
Other features						

N, normal; ↑, concentration raised.

*To convert pg/ml to nmol/l: ×0.005988.

who was diagnosed at the same time as he was being investigated. There were no positive family histories of multiple endocrine neoplasia syndromes.

At presentation all 10 children had raised 24 hour urinary vanillylmandelic acid concentrations. Plasma noradrenaline concentrations were also raised in the eight children measured. Case 7, the child with multiple paragangliomata, had repeatedly normal urinary vanillylmandelic acid concentrations after the removal of her first two tumours but raised plasma noradrenaline concentrations.

Plasma renin activity was raised in four out of eight patients on presentation and six of the eight had raised plasma calcitonin concentrations (normal <0.08 µg/l), but these were normal when repeated postoperatively. Associated with a raised plasma calcitonin concentration, the six patients were noted to be hypercalcaemic at presentation (normal <2.6 mmol/l corrected); postoperatively they were normocalcaemic. Plasma concentrations of parathyroid hormone were high in two of seven children at presentation but fell to normal after removal of their phaeochromocytoma.

Table 3 shows the localisation techniques that were used in our patients. Case 1, who presented in 1960 for investigation, had a phaeochromocytoma clinically diagnosed and underwent

intravenous pyelography, which failed to localise the tumour, and then proceeded to an exploratory laparotomy.

MANAGEMENT

All patients required treatment for their hypertension on presentation as shown in table 2. Six children were successfully treated with a combination of phenoxybenzamine (1–4 mg/kg/day) and propranolol (1–10 mg/kg/day) alone. Case 1 was prepared for surgery with phentolamine (100 µg/kg intravenously). Treatment with labetalol alone in cases 6, 8, and 10 did not produce adequate α blockade and so their treatment was changed. Four of the present series were treated with nifedipine (0.5–4 mg/kg/day). In one child (case 8) nifedipine was added to the regime of propranolol and phenoxybenzamine to achieve adequate catecholamine blockade. In case 10 nifedipine alone was insufficient to block the patient's symptoms and control the blood pressure, this was only achieved when phenoxybenzamine and labetalol were introduced. In two patients (cases 7 and 9) adequate preoperative control of blood pressure was achieved with nifedipine alone.

All 10 children were successfully treated by surgical removal of their paragangliomata. There were no operative complications and no

Table 3 Radiological techniques used to localise catecholamine secreting tumours in the 10 patients

	Case No									
	1	2	3	4	5	6	7	8	9	10
Intravenous pyelography	—	+	—	—	—	+	—	±	±	+
Ultrasound	—	—	—	—	—	—	—	±	±	+
Computed tomography	—	—	—	—	—	—	—	±	±	+
¹²³ I-MIBG scan	—	—	—	—	—	—	+	+	±	+
Selective arteriography	—	+	+	+	+	+	+	+	±	+
Serial catecholamine sampling	—	—	—	+	+	+	+	+	±	+

+, Technique helped localise the tumour; —, technique failed to localise the tumour; ±, equivocal result; * MIBG scan localised the tumours present at initial presentation only but was unhelpful when subsequent tumours were investigated.

Case 7	Case 8	Case 9	Case 10
15.7 Female Headaches, pallor	8.9 Male Headaches, sweating	11.6 Male Headaches	12 Female Found hypertensive at routine clinic visit
↑	↑	↑	↑
4147	12 975	22 039	5243
N	↑	↑	↑
—	N	↑	N
2.65 Phenoxylbenzamine, propranolol, nifedipine	2.56 Labetalol, Phenoxylbenzamine, propranolol, nifedipine	2.87 Nifedipine	2.56 Nifedipine, labetalol, phenoxylbenzamine
Bilateral adrenal +4 extra-adrenal +carotid body tumour	Right adrenal 3.5×4.5	Bilateral adrenal 1.3×1.0 (left) 2.3×2.3 (right)	Left adrenal 7×5.5
		Family history positive	Family history positive, history of right nephrectomy for Wilms' tumour

deaths. Two patients underwent bilateral adrenalectomies (cases 7 and 9). Both subsequently required adrenal replacement treatment with hydrocortisone and fludrocortisone. Case 9 underwent reimplantation of adrenal cortex into his forearm musculature but four months after operation there were no signs of cortisol release with adrenocorticotrophic hormone stimulation. One child (case 10), who had had previous surgery for a stage IV Wilms' tumour involving nephrectomy and adrenalectomy, and had a subsequent adrenalectomy for her phaeochromocytoma, is also on adrenal replacement treatment.

Our children have been followed up for 1.3–10 years (mean 5.3 years), they are all well, none has any evidence of a recurrence, and no patient has developed a multiple endocrine neoplasia syndrome.

Discussion

Paragangliomata are reported to occur more commonly in boys before adolescence^{1 6 7}. Stackpole *et al*, in their review of 100 cases in childhood, reported a male:female ratio of 2:1.¹ In adults the reverse is true with paragangliomata in women being seen more commonly after adolescence.⁸ In the 10 children discussed here there was a preponderance of girls with a ratio boys:girls of 4:6.

Extra-adrenal and multiple paragangliomata are reported to be more common in childhood than in adults. Stackpole *et al* reported, an incidence of 31% and 32% respectively,¹ compared with an incidence of 10% extra-adrenal and 4% bilateral adrenal tumours reported by Melicow in adults.⁸ Eight out of 10 of our children, however, had solitary tumours, which were all intra-adrenal (five right and three left). One child (case 9) had bilateral adrenal tumours and case 7 had multiple extra-adrenal and bilateral adrenal paragangliomata.

In 1974 Glenner and Grimley proposed a system for the classification of paraganglia.³ They recommended that the term phaeochromocytoma be limited to paragangliomata arising in the adrenal medulla. Paraganglia and the paragangliomata arising from them are, in their classification, divided into four 'families' on the basis of anatomical location, histochemical features, and innervation. (1) *Branchiomeric (chemodectomas)*—associated with arterial vessels and cranial nerves of the ontogenetic branchial arches. (a) Intercarotid (carotid body); (b) jugulotympanic (glomus jugulare, glomus tympanicum); (c) orbital; (d) laryngeal; (e) subclavian; (f) aorticopulmonary; (g) coronary; and (h) pulmonary. (2) *Intravagal*. (3) *Aortico-sympathetic*—associated with the sympathetic chain and the retroperitoneal ganglia. In the abdomen (including the organ of Zuckerkandl), thorax, and neck. (4) *Visceral-autonomic*—(a) atria of the heart; (b) urinary bladder; (c) liver hilum; and (d) mesenteric vessels.

The older classification based on chromaffin staining is unsatisfactory because staining is frequently unpredictable and chromaffin positivity of a paraganglioma does not correlate reliably with catecholamine production.^{3 9}

Branchiomeric paraganglia, which are more commonly chromaffin negative and non-functioning, are rare in childhood. In the series of Stackpole *et al* only one in 100 children had an associated non-chromaffin positive paraganglioma in addition to a phaeochromocytoma. This was in a 12 year old boy who seven years after removal of an intra-abdominal and a thoracic paraganglioma, at the age of 19 years, was found to have a carotid body tumour.¹ Revak *et al* reported a 36 year old man with bilateral carotid body tumours who had had a phaeochromocytoma resected at the age of 11 years.¹⁰ Carotid body tumours in isolation occur commonly in the third to sixth decades of life and are only rarely reported in children—in a 1986 review of carotid body tumours by Dickinson *et al* only one of 32 cases was less than 16 years old.¹¹

Familial phaeochromocytomata are well recognised. In the review of Stackpole *et al*, 9% of cases had a positive family history,¹ and in that of Kaufman *et al* in 1983 of phaeochromocytomata at the Mayo clinic, 31% of cases were familial.⁷ Familial occurrence may or may not be associated with multiple endocrine neoplasia syndromes or with neurocutaneous syndromes (neurofibromatosis, von-Hippel Lindau). In multiple endocrine neoplasia syndromes there is a high incidence of bilateral adrenal phaeochromocytomata.¹² Inheritance in familial cases is by mendelian dominant transmission with variable penetrance.¹³ No child in the present series had evidence of a multiple endocrine neoplasia syndrome.

Raised plasma renin activity in association with phaeochromocytomata has been previously described.^{6 14 15} Reports of the association of renal artery stenosis with phaeochromocytomata have appeared in the literature since 1963 when Rosenheim *et al* observed unilateral renal ischaemia due to compression of a renal artery by a phaeochromocytoma.¹⁴ Hiner *et al* in 1976

reported a raised plasma renin activity as well as catecholamines in an 11 year old girl¹⁵; an intra-adrenal tumour was removed, which was not found to be compressing the renal artery or the kidney. Both catecholamines and plasma renin activity fell to normal after surgery. Before surgery haemodynamic studies indicated that there was reduced renal cortical blood flow and fractional flow to the outer cortex consistent with the effects of catecholamines or with those of angiotensin. A 9.5 year old girl was reported by Robinson *et al* in 1973 who was found to have a renal artery stenosis independent of her phaeochromocytoma and not due to compression or haemodynamic effects.⁶ These reports suggest that high plasma renin activity in the presence of a phaeochromocytoma may be due to one or more of several factors: (i) ischaemia secondary to volume depletion caused by excess catecholamines, (ii) compression of a renal artery by the tumour, (iii) intrinsic renal artery diseases, and (iv) intrinsic renal parenchymal disease.⁸ Four children in the present series were found to have raised plasma renin activities at presentation. In one child (case 10) this was presumed to be due to the pressure of a large adrenal phaeochromocytoma on the upper pole of the kidney causing distortion of the upper pole artery on the arteriogram; in the other three cases the intra-adrenal tumours were felt to be too small to be causing a pressure effect. One of these patients did not have arteriography and so we cannot exclude a renal artery stenosis in him, but in all four children the plasma renin activity fell to normal after surgery.

Reliance on urinary determinations of vanillylmandelic acid excretion can be misleading in paragangliomata. The amounts of free catecholamines and their metabolites vary depending on the levels of synthesising and metabolising enzymes within the tumour and the excretory function of the kidneys.¹⁶ These factors may account for the false positive and negative results that are reported. In addition, in children, 24 hour urinary collections are difficult and cumbersome to obtain and are not always possible. Plasma catecholamine concentrations have the highest sensitivity for diagnosing paragangliomata; urinary vanillylmandelic acid concentrations are the least sensitive tests.¹⁷ Plasma catecholamines should be obtained under standardised, controlled conditions, however, which are often difficult to achieve in children. It has been suggested, in adults, that a raised plasma adrenaline may be used as a marker for distinguishing between adrenal and extra-adrenal tumours as the adrenal medulla is the principal source of adrenaline and so, theoretically, both plasma adrenaline and noradrenaline concentrations should be measured.¹⁸ In practice, however, we found that the seven children in our series with adrenal tumours whose plasma noradrenaline concentrations were measured, had appreciably raised values. Case 7 had raised noradrenaline concentrations before removal of both her intra-adrenal and extra-adrenal tumours.

We did not find it necessary to perform pharmacological tests on our patients to make the diagnosis of phaeochromocytoma and would

view them as being potentially dangerous procedures to undertake.

The localisation techniques that were used in our 10 cases have already been outlined in table 3. The current literature suggests that the use of computed tomography should all but eliminate the need for potentially hazardous arteriographic studies in the preoperative detection and localisation of paragangliomata.¹⁹ This has not been our experience nor that of others.²⁰ Ultrasound and computed tomography were only helpful in localising large tumours. In only three of the eight patients who had an ultrasound scan was the scan positive. For two patients, who initially had negative scans, when their tumours were localised by other means, repeating the ultrasound scan allowed the phaeochromocytomata to be visualised. Computed tomography was positive in two of five patients only and missed a 5 cm diameter tumour in one case.

The recently introduced meta-iodo-benzyl guanidine (MIBG) scanning for localising catecholamine producing tumours was not the most sensitive investigation in our patients. We used ¹²³I instead of ¹³¹I labelled MIBG as this decreases radiation exposure and increases the sensitivity of the scan.²¹ Using ¹²³I-MIBG, however, normal adrenal glands are visualised and in our patients it has been difficult to distinguish increased MIBG uptake in an abnormal gland from normal adrenal MIBG uptake particularly in one child (case 9) who had bilateral adrenal phaeochromocytomata. Case 7 had a positive MIBG scan at presentation (fig 1) but subsequently MIBG scanning was unhelpful because her paragangliomata were either intra-adrenal or anatomically situated very near her adrenals. The MIBG scan was unable to distinguish these tumours from normal adrenal glands. A review of the use of MIBG scanning in 400 cases concluded that, in the case of sporadic intra-adrenal lesions MIBG scanning is probably no better than a computed tomogram but is superior for localising extra-adrenal, recurrent, and malignant lesions.²¹

Although invasive and time consuming we

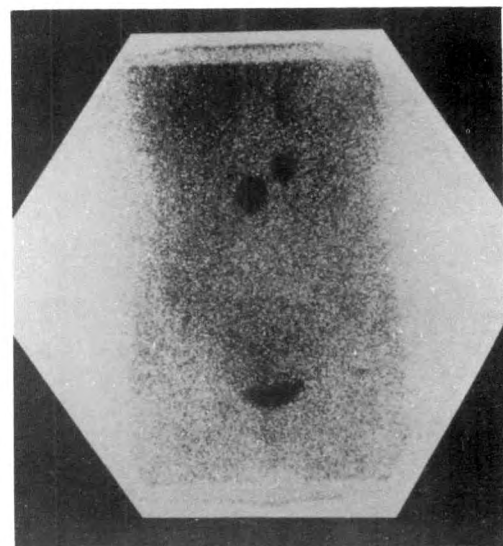


Figure 1 Case 7: MIBG scan showing the presence of two para-aortic paragangliomata.

found arteriography and venous catecholamine sampling to be the most helpful investigations for localising tumours. In all eight children who underwent arteriography the tumours were localised. Sampling was very helpful and localised the tumours in six out of seven children studied. In one child (case 9) sampling was positive but because he had bilateral adrenal phaeochromocytomata it was difficult to localise precisely the sources of catecholamine production. In another (case 7) sampling was particularly helpful in localising her multiple tumours (figs 2 and 3). In one child (case 3) arteriography and sampling enabled us to identify a 0.3 cm intra-adrenal phaeochromocytoma that had not been identified by other means.

Preoperative control of the hypertension in patients with phaeochromocytomata is very important, both for definitive surgery and arteriography. Perioperative deaths have usually resulted from inadequate preoperative preparation and blood pressure control.²² The treatment for phaeochromocytomata has traditionally involved the use of α and β sympathomimetic blocking agents: usually phenoxybenzamine and propranolol. Five of our children have been

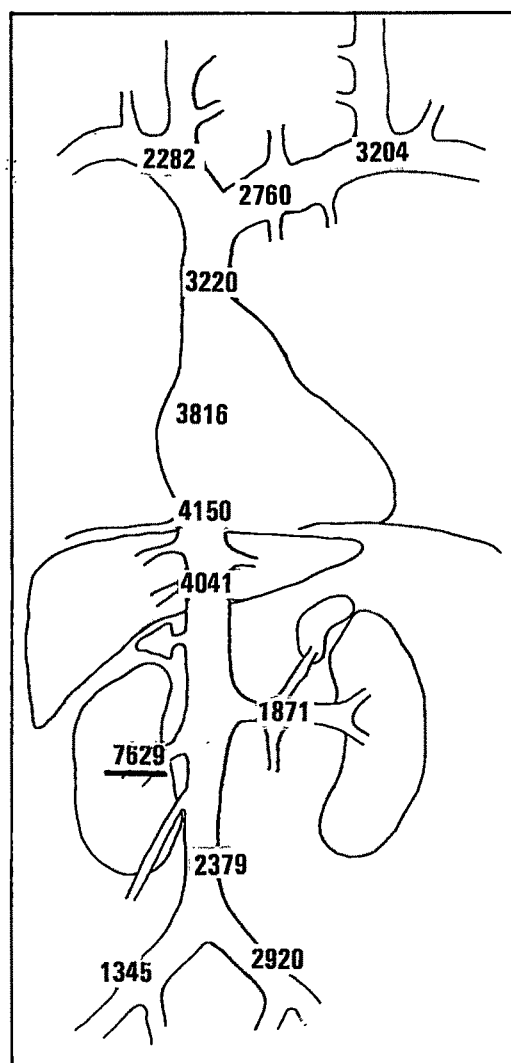


Figure 2 Case 7: noradrenaline sampling data showing high concentrations from the main right renal vein. A tumour was subsequently removed from the right para-adrenal region. Results are in pg/ml; to convert to nmol/l, $\times 0.005988$.

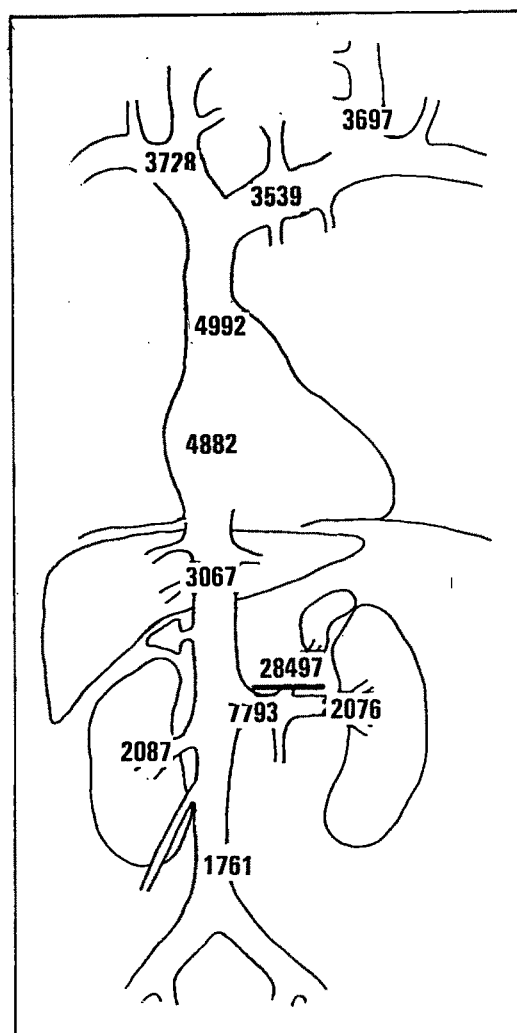


Figure 3 Case 7: noradrenaline sampling data showing high concentrations from the left adrenal vein. A left intra-adrenal phaeochromocytoma was removed subsequently. Results are in pg/ml; to convert to nmol/l, $\times 0.005988$.

successfully treated with this combination alone preoperatively. More recently labetalol, which has both α and β blocking activity, has been used in the management of phaeochromocytomata.²³ Oral labetalol was used in three of our children but did not produce adequate α blockade and so their treatment was changed. Recently interest has grown in the use of nifedipine in the management of catecholamine excess states. Serfas *et al* first reported the suppression of symptoms by nifedipine in a patient with hypertrophic cardiomyopathy and a phaeochromocytoma.²⁴ Symptom relief was associated with a fall in plasma noradrenaline concentrations suggesting that nifedipine blocked the release of noradrenaline from phaeochromocytomata. A second report by Lenders *et al* postulated that nifedipine blocked the peripheral action of noradrenaline by exhaustion of intracellular calcium stores after chronic noradrenaline stimulation in a patient with a bladder paraganglioma.²⁵ Four of the present series were treated with nifedipine; however, in only two of the children was adequate preoperative control of their blood pressures achieved with nifedipine alone.

Paragangliomata are rare in childhood and

hence experience in any one institution is limited. Our experience of 10 cases differs in some respects from that previously reported with a lower incidence of extra-adrenal and multiple tumours. Despite recent advances in radiological techniques for localising tumours we have continued to find arteriography and catecholamine venous sampling to be the most sensitive techniques for localising tumours and for providing important preoperative surgical information regarding the vascular supply of a tumour. The use of nifedipine in the preoperative preparation of our most recent cases has been encouraging, although in most cases phenoxybenzamine and propranolol remain the drugs of first choice for catecholamine blockade. Case 7 illustrates the importance of close follow up for further tumours and the association of other tumours of the paraganglia system in the same patients.

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Hypertension after renal transplantation in patients treated with cyclosporin and azathioprine

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Abstract

The incidence of hypertension was sought in 102 children who had undergone renal transplantation. Fifty five were being treated with cyclosporin and 47 with azathioprine, and they were followed up for a maximum of five years. After one year 35 of those receiving cyclosporin (64%) and 34 of those receiving azathioprine (72%) were hypertensive; after five years the figures were 5/6 (83%) and 25/35 (71%), respectively. Recipients of grafts from living related donors had a lower incidence of hypertension than recipients of cadaveric grafts. The incidence of hypertension was higher in patients with acquired original kidney disease than in children with congenital or familial diseases. In both groups creatinine clearance and the frequency of acute rejection episodes did not differ between normotensive and hypertensive patients. When the lowest concentrations of cyclosporin in whole blood were more than 400 ng/ml the incidence of hypertension one year after transplantation was higher. The incidence of hypertension after renal transplantation in children is higher than that reported in adults. Acquired original disease, transplantation of cadaveric grafts, and nephrotoxicity of cyclosporin are all contributory factors.

Hypertension after renal transplantation poses a considerable therapeutic problem to the nephrologist. Transient hypertension immediately after the transplant is found in almost all cases.¹ The main concern, however, is persistent hypertension with cardiovascular and cerebrovascular complications, and increased mortality and morbidity.^{2,3} The aim of the present study was to investigate the incidence and possible causes of hypertension after transplantation in children and adolescents, and to compare two different treatment regimens—cyclosporin and azathioprine.

Patients and methods

One hundred and two patients who received transplants between 1973 and 1987 were studied. Patients with grafts that had been functioning for less than a year were excluded. Seventy two patients who received transplants between 1982 and 1987 were given cyclosporin, but 10 lost their grafts because of irreversible rejection, and surgical and other complications, and seven patients were lost for follow up or received three drugs for immunosuppression (a combination of cyclosporin, azathioprine, and low dose prednisolone). Thus 55 patients could

be evaluated in the cyclosporin study group. Ninety seven recipients were treated with azathioprine alone, and 62 grafts functioned for more than a year. Thirty five organs were lost because of irreversible rejection, thrombosis and recurrence of oxalosis, and 15 patients were lost to follow up. Thus 47 patients receiving conventional immunosuppression with azathioprine and high dose prednisolone could be evaluated.

Our treatment regimens for azathioprine and cyclosporin have been described elsewhere.^{4,5} The mean (SD) age at the time of renal transplantation was 11.7 (3.4) years in the azathioprine group and 12.4 (4.0) years in the cyclosporin group. Histories were obtained from the case notes, and included information about hypertension before transplantation, and previous treatment with steroids. Hypertension was defined as persistent blood pressure readings above the 95th percentile (according to Horan *et al*⁶) that required antihypertensive treatment. Severe hypertension was defined as blood pressure readings necessitating treatment with three or more antihypertensive drugs in maximum or near maximum dosage.

Antihypertensive regimens varied, and the following drugs were used in a 'stepped care' approach: propranolol (dose range: 0.8–5.8 mg/kg/day), hydralazine (dose range: 0.9–5.9 mg/kg/day), nifedipine (dose range: 0.2–1.8 mg/kg/day), and α -methyldopa (dose range: 9–52 mg/kg/day). Two patients in each group were also given captopril (dosage range: 0.5–2.1 mg/kg/day). One patient with a membranoproliferative glomerulonephritis had a decreased glomerular filtration rate, but none of the others showed deterioration of renal function after taking captopril. Most of the patients received additional frusemide (dose range after the initial period of six weeks after transplantation: 0.9–6.2 mg/kg/day). Chest radiographs, electrocardiograms, and ophthalmic examinations were assessed for symptoms suggestive of hypertension.

Serum creatinine and sodium concentrations were measured by standard procedures, and urinary sodium excretion was calculated and correlated with body weight. Creatinine clearance was calculated by the method of Schwartz *et al*,⁷ which is appropriate for children who have received transplants.⁸ Cumulative doses of prednisolone were documented for each patient for each observation interval.

The Mann-Whitney U test, Student's *t* test, and Fisher's exact test were used to assess the significance of differences between and within groups. Values are given as mean (SD), or median and 95% confidence interval (CI).

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Table 1 Original diseases in recipients of renal transplants

	Patients treated with cyclosporin (n=55)	Patients treated with azathioprine (n=47)
No (%) with congenital or familial renal disease:	38 (69)	31 (66)
Renal dysplasia or hypoplasia	14	10
Familial juvenile nephronophthisis	8	5
Oxalosis	0	1
Cystinosis	5	9
Obstructive uropathy	8	1
Familial nephritis	2	4
Infantile polycystic kidney	1	1
No (%) with acquired renal disease:	17 (31)	16 (34)
Proliferative glomerulonephritis	3	3
Focal segmental glomerulosclerosis	3	2
Haemolytic uraemic syndrome	4	6
Miscellaneous	7	5

Results

The distribution of original kidney diseases in the study groups is shown in table 1. About two thirds of the patients had congenital or familial diseases; there were no differences between the two treatment groups. The overall incidence of hypertension after transplantation is shown in table 2; there was no significant difference between the study groups. No change of incidence was seen in the azathioprine group during the five years of observation, whereas in the cyclosporin group the percentage apparently increased slightly. The difference between the first and fifth year, however, was not significant.

The incidence of severe hypertension requiring treatment with at least three antihypertensive drugs was higher among those receiving cyclosporin than among those taking azathioprine (table 3). In the azathioprine group there was only one patient who required more than

two hypotensive drugs during the period two to four years after transplantation, but the difference was not significant.

Ten patients receiving cyclosporin and 17 receiving azathioprine received allografts from living related donors, the remainder receiving cadaveric grafts. Hypertension was significantly more common in recipients of cadaveric grafts who were taking azathioprine during the first two years after transplantation, and during the first three years in those taking cyclosporin (table 4). The difference persists during the following years, but seems to level off.

Bilateral nephrectomy was not routinely performed in our patients, but in a few (six taking cyclosporin and three taking azathioprine) bilateral nephrectomy was done before transplantation because of obstructive uropathy (n=4), infantile polycystic disease (n=2), or severe hypertension (n=3). In some other cases nephrectomy was done after transplantation, mainly because of severe hypertension. The incidence of hypertension in the small group of patients after bilateral nephrectomy is shown in table 5. Most of the patients remained hypertensive.

The role of the original disease that lead to endstage renal failure in causing hypertension after transplantation is shown in table 6. Acquired original kidney diseases were associated with hypertension more often than congenital or familial diseases. The difference was significant in the first year in children treated with azathioprine (table 6).

The cumulative prednisolone dose received by each patient each year is shown in fig 1. The mean dose in the azathioprine group was about

Table 2 Overall incidence* hypertension in the two groups before, and up to five years after, transplantation

	Before transplantation	Years after transplantation				
		1	2	3	4	5
Patients receiving cyclosporin	39/55 (71)	35/55 (64)	25/36 (69)	16/25 (64)	11/15 (73)	5/6 (83)
Patients receiving azathioprine	34/47 (72)	34/47 (72)	32/44 (73)	32/42 (73)	30/39 (77)	25/35 (71)

*No with hypertension/total No of patients.

Table 3 Incidence* of severe hypertension in the two groups up to five years after transplantation

	Years after transplantation				
	1	2	3	4	5
Patients receiving cyclosporin	4/55	3/36	2/25	2/15	1/6
Patients receiving azathioprine	0/47	1/44	1/42	1/39	0/35

*No with severe hypertension/total No of patients. The results were not significant.

Table 5 Incidence* of hypertension in patients who underwent bilateral nephrectomy before investigation

	Years after transplantation				
	1	2	3	4	5
Patients receiving cyclosporin	3/6	3/5	1/3	1/2	1/2
Patients receiving azathioprine	3/3	2/3	2/3	2/3	—

*No with hypertension/total No of patients.

Table 4 Incidence* of hypertension in patients with cadaveric kidneys compared with that among patients with kidneys from living related donors

	Years after transplantation				
	1	2	3	4	5
Patients receiving cyclosporin:					
No (%) with cadaveric kidneys	33/45 (73)	24/30 (80)	15/20 (75)	9/12 (75)	3/3 (100)
No (%) with kidneys from living related donors	2/10 (20)	1/6 (17)	1/5 (20)	2/3 (67)	2/3 (67)
p Value	<0.01	<0.01	<0.05	1.0	1.0
Patients receiving azathioprine:					
No (%) with cadaveric kidneys	25/30 (83)	23/27 (85)	22/26 (85)	20/24 (83)	17/22 (77)
No (%) with kidneys from living related donors	9/17 (53)	9/17 (53)	10/16 (63)	10/15 (67)	8/13 (62)
p Value	<0.05	<0.05	0.2	0.4	0.5

*No with hypertension/total No of patients.

Table 6 Incidence* of hypertension in patients with acquired kidney disease compared with that among patients with congenital or familial kidney disease

	Years after transplantation				
	1	2	3	4	5
Patients receiving cyclosporin:					
No (%) with acquired kidney disease	12/17 (71)	10/13 (77)	6/8 (75)	4/5 (80)	1/1 (100)
No (%) with congenital kidney disease	23/38 (61)	15/23 (65)	10/17 (59)	7/10 (70)	4/5 (80)
p Value	0.7	0.7	0.7	1.0	1.0
Patients receiving azathioprine:					
No (%) with acquired kidney disease	15/16 (94)	13/15 (87)	13/15 (87)	12/14 (86)	10/13 (77)
No (%) with congenital kidney disease	19/31 (61)	19/29 (66)	19/27 (70)	18/25 (72)	15/22 (68)
p Value	<0.05	0.3	0.4	0.6	0.9

*No with hypertension/total No of patients.

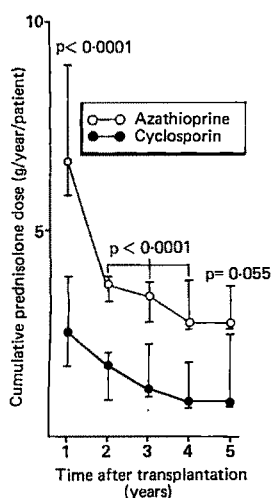


Figure 1 Cumulative prednisolone doses in patients receiving treatment with azathioprine and cyclosporin. Values are given as median and 95% confidence intervals.

twice as high as that received by the cyclosporin group. This difference is highly significant during the first four years. Comparing hypertensive and normotensive patients in each group separately, however, there was no correlation between hypertension with dose of prednisolone.

Graft function was assessed by calculation of the creatinine clearance from plasma creatinine concentration and body length. The creatinine clearance declined in both groups over the five years, but was significantly lower in the cyclosporin group compared with the azathioprine group (fig 2). Patients in the two groups were compared, measurements of glomerular filtration rate below 30 ml/min/1.73m² were associated with higher rates of hypertension (table 7).

The influence of cyclosporin on the development of hypertension was assessed by studying the concentrations of cyclosporin in the blood of both normotensive and hypertensive patients (fig 3); the mean concentrations were slightly higher in the hypertensive patients, but the difference was not significant. High concentrations of cyclosporin in blood were associated with a higher incidence of hypertension a year after transplantation (table 8).

The incidence of abnormal findings on chest radiography, ophthalmoscopy, and electro-

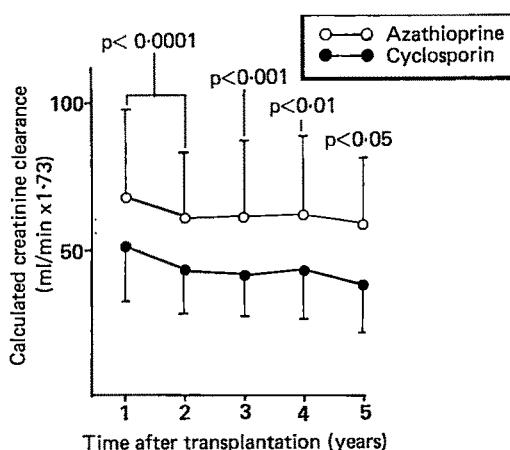


Figure 2 Graft function expressed as creatinine clearance in the two groups. Values are given as mean (SD).

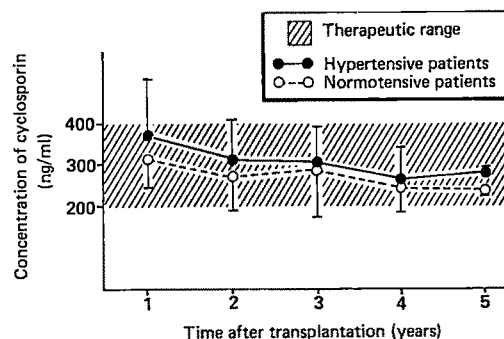


Figure 3 Cyclosporin concentrations in whole blood in normotensive and hypertensive patients projected on to the therapeutic range. Values are given as mean (SD).

cardiography in recipients of transplants is shown in table 9. Retinal and electrocardiographic features of hypertension were consistently seen in 40–60% of patients. Radiological signs (vascular congestion and increased transverse cardiac diameter) decreased over the first two years and by five years were seen in only 16% of patients. There were no significant differences between normotensive and hypertensive patients within each group concerning daily urinary sodium excretion, urinary volume, and the number of acute episodes of rejection.

Hyper-reninism or complications of the graft's vascular anastomosis, or both, were found in four patients of the cyclosporin group and five patients of the azathioprine group. They were not serious and no specific measures were taken to correct the stenosis. Two children treated with cyclosporin and one treated with azathioprine experienced recurrence of original disease (membranoproliferative glomerulonephritis); all three were hypertensive.

Discussion

The incidence of hypertension after renal transplantation is generally reported to be higher in children and adolescents than in adults. Almost all the children who received renal transplants became hypertensive in the first few weeks after

Table 7 Incidence* of hypertension in patients with glomerular filtration rate above and below creatinine clearance of 30 ml/min/1.73 m²

	Years after transplantation				
	1	2	3	4	5
No (%) with glomerular filtration rate ≤ 30	8/9 (89)	8/9 (89)	7/10 (70)	9/9 (100)	4/4 (100)
No (%) with glomerular filtration rate > 30	61/93 (66)	49/71 (69)	41/57 (72)	32/45 (71)	26/37 (70)

*No with hypertension/total No of patients. The results were not significant.

Table 8 Incidence* of hypertension in patients treated with cyclosporin. Those with high concentrations in whole blood (>400 ng/ml) are compared with those with low concentrations (<400 ng/ml)

	Years after transplantation				
	1	2	3	4	5
No (%) with concentrations <400 ng/ml	25/44 (57)	19/29 (66)	14/22 (64)	10/14 (71)	4/5 (80)
No (%) with concentrations >400 ng/ml	10/11 (91)	6/7 (86)	2/3 (67)	1/1 (100)	1/1 (100)
p Value	<0.05	0.6	1.0	1.0	1.0

*No with hypertension/total No of patients.

Table 9 Incidence* of other findings indicating past or present hypertension in recipients of renal transplants

	Years after transplantation				
	1	2	3	4	5
No (%) with electrocardiographic changes	43/71 (61)	22/55 (40)	26/49 (53)	15/36 (42)	11/28 (39)
No (%) with radiological changes	18/61 (30)	9/52 (17)	10/53 (19)	7/36 (19)	4/25 (16)
No (%) with retinal changes	22/53 (42)	14/34 (41)	12/30 (40)	12/21 (57)	10/24 (42)

*No of abnormal findings/total No of examinations.

transplantation,¹ whereas hypertension in the same period in adults occurs in about 80%.⁹ Persistence of hypertension in adult patients occurs in about half.²⁻⁹ In a large series of children undergoing transplantation and treated with azathioprine Broyer *et al* found an incidence of late hypertension of 65%,¹⁰ and sustained hypertension in children has been reported in up to 86%.³ Our data confirm these findings (table 2). A slight but not significant increase in the development of hypertension over the years can be noted in the cyclosporin group. The incidence in the azathioprine group remained within the range 72–77%. The incidence of hypertension was higher in patients who received cadaveric grafts than in those who received grafts from living related donors in both study groups (table 4), particularly among those in the cyclosporin group during the first three years after transplantation. These findings accord with those of other investigators.⁹⁻¹¹ The beneficial effect of organs from living related donors could be related to fewer immunological injuries at vascular and parenchymal sites, or to shorter ischaemic time of the graft, or both.¹²

The results of investigation of the influence of original disease on hypertension after transplantation are conflicting. Though some authors have reported a similar incidence of hypertension in congenital and glomerular diseases,⁹⁻¹⁰⁻¹² others have found a stronger association between hypertension and glomerular diseases.¹⁻³ We classified our cases as congenital or familial, and acquired, diseases. Our findings support the idea that acquired diseases, assuming that they were associated with pathoimmunological mechanisms, are more often followed by hypertension after transplantation (table 6). Most of these patients had received steroids before transplantation. Recurrence of the original disease was the cause of the hypertension in three children.

Our data do not show clearly the beneficial effect of bilateral nephrectomy on the development of hypertension because there were too few cases for statistical evaluation (table 5). The effect of removal of the kidneys has, however, been thoroughly studied. Curtis *et al* investigated six patients before, and a mean (SD) of

4.5 (1.5) months after, bilateral nephrectomy.¹³ They found that blood pressure fell and renal vascular resistance dropped. Renal plasma flow of the graft rose 77% at the same time. Other authors have confirmed these results.⁹⁻¹⁴⁻¹⁵ Renin hypersecretion of the patients' own remaining kidneys is thought to be the main mechanism.⁹⁻¹⁴⁻¹⁵ This is in accord with the observation that patients with uncontrollable hypertension on haemodialysis respond to nephrectomy.¹⁶

Hypertension as a result of long term steroid treatment is a well known feature. Some studies have shown a significant drop in blood pressure after switching to taking them on alternate days, the total dose remaining the same.¹⁰⁻¹⁷⁻¹⁸ Patients taking conventional immunosuppression with azathioprine and high dose prednisolone are particularly at risk of developing steroid associated hypertension. As shown in fig 1, patients treated with azathioprine received significantly more steroids. We therefore regard treatment with steroids as an important contributory factor to the development of hypertension in conventional immunosuppression. Considering each study group separately, the hypertensive patients did not receive significantly higher cumulative doses of prednisolone.

It has been reported that normotensive recipients of grafts increase their blood pressure when put on a high sodium diet.¹⁴ Thus the intake of sodium may also be a contributory factor. The daily sodium intake (as assessed by the daily urinary sodium excretion) was not higher in our hypertensive patients. With an assumed sodium intake of 3–5 mmol/kg/day, our patients were receiving a normal amount of sodium.

Renal artery stenosis can be the result of endothelial damage, atheromatous plaques, trauma during harvest and transplantation, disturbed haemodynamics during the end to side anastomosis, and immunological damage.¹⁶ Broyer *et al* found a total incidence of 43/334 (13%) of appreciable stenoses in children who had received transplants, and 20% in grafts in hypertensive patients.¹⁰ Henrikson *et al* detected 22/367 (6%) in a series of adult patients; nine of the 22 were normotensive.¹⁹ In

our series four cases had mild to moderate renal artery stenosis.

The effects of cyclosporin on renal function have been the subject of numerous investigations. Continuous cyclosporin treatment leads to chronic vasoconstriction of the renal microvasculature.⁹⁻²⁰ This is partly mediated through increased sympathetic nerve activity and inhibited renal prostaglandin synthesis, and partly through stimulation of the renin-angiotensin system.²¹ Renal vascular resistance and arterial blood pressure are increased in consequence. In cardiac graft recipients receiving cyclosporin for more than 12 months, these effects are rarely reversible and potentially progressive.²⁰ Switching from cyclosporin to azathioprine after a certain period has been reported to cause a fall in renal vascular resistance and arterial blood pressure.⁹⁻²² More recent data indicate that hypertension in patients treated with cyclosporin may be associated with a defect in renal sodium excretion.²³⁻²⁴ The effect of dietary sodium restriction and antihypertensive treatment may thus be more pronounced in hypertension associated with cyclosporin. As an obvious sign of the influence of cyclosporin on the renal microvasculature, creatinine clearance was significantly compromised in the cyclosporin group (fig 2). The decline in renal function over five years, however, was parallel in the two groups. This indicates the existence of other factors in the azathioprine group. Figure 3 shows that hypertensive patients had slightly higher cyclosporin concentrations, although there was no significant difference. A higher percentage of patients with cyclosporin concentrations of more than 400 ng/ml were hypertensive (table 8). As doses of cyclosporin were reduced, the number of concentrations over 400 ng/ml decreased. There were therefore too few data to evaluate the influence of high cyclosporin concentrations after three years. The percentage of severe hypertension was higher in recipients treated with cyclosporin, indicating that cyclosporin has a role in the pathogenesis of hypertension (table 3).

Chronic rejection has been reported as a cause of hypertension in renal recipients of allografts in about 15% of adults,¹⁹ and 59% in children.¹⁰ Ingelfinger *et al* found a positive correlation between blood pressure, renal function, and the number of antihypertensive agents administered. They interpreted these results as an effect of chronic rejection.¹ In our study the creatinine clearance was not significantly lower in hypertensive patients than in normotensive patients. Glomerular filtration rate declined in both treatment groups, however. It may be that chronic rejection leading to progressive impairment of graft function could also be a cause of hypertension.

The long term outcome of renal transplantation depends on the control of hypertension. Strict observation on consistent treatment of the patients are therefore necessary. Our antihyper-

tensive regimen varied; nowadays we start with frusemide because the renal function is usually reduced. If necessary, we then add nifedipine as a vasodilator. If there is tachycardia, β -adrenergic antagonists (for example, propranolol) are considered. We may then give an additional vasodilating agent (for example, hydralazine). Converting enzyme inhibitors (such as captopril) are used in refractory hypertension if renal function remains stable after an initial dose. Subsequent doses and intervals between them are adjusted according to the renal function.

The Statistical Package for the Social Sciences (x) software was supplied by SPSS Inc.

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Symptoms in 298 infants under 6 months old, seen at home

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Abstract

Symptoms were assessed in 298 infants under 6 months old seen at home. Their mothers were asked if they were concerned about their babies and then questioned about the presence, duration, and severity of 28 predefined symptoms. Forty seven mothers expressed concern about their babies (16%), whereas on direct questioning 241 (81%) reported symptoms present within the last 24 hours. One hundred and twenty three (41%) reported three or more. Many of the symptoms occurred in more than 15 babies (5%). The commonest were cold peripheries (117, 39%), noisy breathing (88, 30%), and rash (68, 23%). These had often been present for many days. Only 257/819 reported symptoms (31%) were of recent onset (<4 days) with 168 (21%) graded by the mother as moderate or severe. A few highly specific symptoms that were associated with serious conditions were rare. Symptoms cannot be interpreted without detailed questioning taking their severity and duration into account, and most occur too often to be used as indicators for referral.

After the neonatal period, there is a higher incidence of illness and death in the first six months than in the rest of childhood. It has been suggested that earlier recognition of important symptoms in young babies, and early treatment, might reduce the severity of illness and prevent some deaths.^{1 2} The multicentre study of post-neonatal mortality investigated 297 infants with signs of illness in the days immediately before death and concluded that 24% of the families had acted 'inappropriately' in the management of their child's illness by not recognising that the child was seriously ill or by failing to seek help.³ The general practitioner was contacted in only 131 cases, but in 64% was deemed to have managed the case 'inadequately'. There was a 'delay in diagnosis' or 'inappropriate treatment' in 26% of the babies admitted to hospital.

To facilitate the recognition of serious illness Stanton *et al* highlighted 12 'major' symptoms, which needed medical attention the same day.⁴ The paper was criticised because the symptoms were considered to be too common to be useful predictors.⁵⁻⁸ Valman subsequently suggested four 'undoubtedly sinister' symptoms that warranted an opinion from a paediatrician in an infant under 6 months old.⁹ A further study in general practice, however, suggested that at least two of these symptoms (poor feeding and difficulty in breathing) were 'too common in infants at home to be regarded as truly sinister'.

¹⁰ This controversy shows the dearth of accurate data about the incidence and severity of symptoms in babies in the community. Studies of symptoms in babies dying suddenly and unexpectedly have used case-control comparisons, but the numbers of controls were relatively small, the symptoms were not well defined, and their severity and duration were not recorded.^{4 11} In studies of babies' symptoms in general practice, information was collected only about babies who were unwell.^{10 12 13} In one study the questions were retrospective and there were variations in what parents and doctors meant by a particular symptom.¹²

The present study is part of a larger project aiming to design a system to help parents and doctors assess the severity of acute illness in babies. Data have also been collected from 709 babies presenting to hospital. Any system that is going to help parents and professionals to decide when a baby's symptoms warrant medical attention must have high specificity in order to avoid increasing both parental anxiety and the workload on the primary health care team. It must therefore take account of the incidence of symptoms within the community. This paper presents data about the incidence, severity, and duration of symptoms in 298 randomly selected infants assessed at home.

Subjects and methods

ENROLMENT OF SUBJECTS

The study aimed to assess 300 infants. Babies were enrolled postnatally at the maternity hospital in Cambridge and were eligible for the study if (i) the baby was born at more than 36 weeks' gestation and was healthy at birth, and (ii) the mother was English speaking and lived within five miles of the hospital. Babies were randomly selected from the birth register. The enrolment schedule ensured an even distribution of assessments across postnatal age (1 to 25 weeks) and season.

In 275 cases the mother who was initially approached agreed to participate. When a mother refused a substitute was randomly selected from other babies born on the same day. Thirteen infants could not be assessed (12 failed to keep the appointment and one died suddenly at home). Twelve were replaced. One mother failed to keep her appointment on the last day of the study. Thus 299 infants were assessed.

ASSESSMENT

Infants between 1 and 25 weeks of age were seen

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Table 1 Definitions of symptoms

Symptom	Definition
Cold peripheries	Hands, feet, or limbs, have felt cold.
Noisy breathing	Persistent noises, including mucousy sounds, snuffles, stridor, grunt or wheeze.
Rash	Appreciable areas of inflammation, or >6 spots (birth marks excluded).
Decreased sleeping	Less sleep than usual, during the day or night.
Runny nose	Mucus seen over the philtrum (not just a blocked nose).
Sweating	Beads of sweat on forehead, or obviously wet hair when at rest or feeding.
Increased sleeping	More sleep than usual during the day or night.
Increased irritability	More fractious and difficult to settle than usual.
Increased crying	Has cried more often or for longer periods than usual.
Cough	More than five episodes of coughing/day.
Feels hot	Has felt hotter than normal.
Pallor	Has looked generally pale.
Not feeding normally	Has taken less fluids or solids, or fed more slowly (the amount of fluid taken was scored in thirds of normal intake).
Vomiting	Forceful regurgitation of a significant quantity of fluid (excluding possetting). The number of vomits of more than half the feed was recorded.
Not himself or herself	Baby has behaved differently from usual.
Diarrhoea	Excessively fluid motions. The number of stools passed during the last 24 hours was recorded.
Abnormal cry	An unusual cry.
Breathing difficulty	Has worked harder to breathe, or had a heaving chest.
Less urine	Fewer wet nappies than usual or nappies that have been drier than usual. If output was reduced, the number of wet nappies was recorded.
Decreased activity	Has been moving arms and legs less than usual.
Drowsy	Less alert than usual. A 'drowsiness score' was then recorded, which allowed a more objective assessment of drowsiness: 'When the baby is awake is he (i) always alert, (ii) occasionally drowsy, (iii) occasionally alert, or (iv) never alert?'
Jaundice	Yellow skin or sclera.
Projectile vomiting	Vomit that travelled more than 45 cm.
Cyanotic episodes	Periods of obvious blueness of the tongue and lips.
Apnoeic episodes	Cessation of breathing for 20 seconds or more.
Bile stained vomiting	Episodes of green vomiting.
Blood in stools	Frank blood mixed with stools (not streaks).
Convulsion	Shaking movements with decreased awareness.

Symptoms were recorded only if they occurred within the previous 24 hours.

at home by one observer (AJT) between 1 April 1986 and 31 March 1987. The mother was asked whether she was concerned about the baby's health, and whether the baby was ill. She was then questioned in detail about 28 symptoms, which were predefined in a study manual (table 1). A symptom was recorded only if it had occurred during the previous 24 hours. The mother was asked about its total duration, how long it had been at its present severity, and her perception of the current severity on a four point scale indicating normal, mild, moderate, and severe (with normal taken as the parent's perception of what is normal for babies generally). Data about the baby's birth and family circumstances were also collected. Details of all hospital admissions, and of medication, immunisations, and consultations with the general practitioner (excluding routine contacts) within specified periods were recorded.

A detailed and standardised examination covering 48 signs was also carried out. At the end of the assessment, the assessor's impression of the degree of illness was recorded on a five point scale indicating well, or mildly, moderately, or severely ill, or requiring resuscitation. The babies were visited on the next three days by a second investigator (JMT) who recorded medical contacts and changes in their conditions.

Results

Of the 299 infants, one was excluded from analysis as he was in hospital at the time of assessment with pneumonia that necessitated mechanical ventilation.

THE STUDY POPULATION

Similar numbers of infants were seen at each month of age and in each season. One baby was

diagnosed as having congenital heart disease after enrolment. Just over half of the babies were girls; 125 (42%) were the only child in the house; in 106 (36%) there was one other child, in 52 (17%) there were two others, and in 16 (5%) there were three or more. Of the parents 254 (85%) were married, 27 (9%) were cohabiting, and 17 (6%) were living alone or with relatives. Fifteen (5%) of the mothers were less than 20 years old, 61 (21%) were 20–24, and 42 (11%) were 35 years or more. The social class distribution was social class I—22%, II—19%, III (non-manual)—9%, III (manual)—27%, IV—14%, and V—2%. In 7% there was insufficient information to code the social class.¹⁴ In nearly half the families at least one parent smoked.

VISITS TO THE DOCTOR IN THE PREVIOUS WEEK
Forty three babies (14%) had been seen by a doctor during the previous week, in four cases more than once. Four babies (1%) were seen on the day of assessment, and two of these had also been seen during the previous week. Four babies (1%) had appointments later that day. One baby had been discharged from hospital on the morning of the assessment.

DRUGS AND IMMUNISATIONS

Eighteen babies (6%) had received antipyretics in the previous 24 hours and nine (3%) had received antibiotics in the previous 72 hours. Fifty five (18%) had been immunised in the previous fortnight, eight (3%) within the previous 24 hours.

ASSESSOR'S IMPRESSION OF ILLNESS

Two hundred and thirty nine babies (80%) were graded as well, and 51 (17%) as mildly ill. Only

eight (3%) were considered moderately ill. Of these, three were under review by their general practitioner for respiratory infections, and one had whooping cough. Two were seen by their general practitioner later the same day; one developed measles, and the other was admitted to hospital eight hours after the assessment with a urinary tract infection and septicaemia. No babies were considered to be seriously ill at the time of the assessment.

MOTHERS' CONCERNS ABOUT THE BABIES' HEALTH

Forty seven mothers (16%) mentioned one or more of 22 different concerns (table 2). Thirty three mentioned one concern, 11 mentioned two, two mentioned three, and one mentioned four. Twenty three mothers (8%) thought their baby was ill at the time of the assessment or had been ill within the last 24 hours.

Table 2 Problems that concerned the mother on initial questioning

Problem	No (%) of babies (n=298)
Noisy breathing	10 (3)
Common cold	10 (3)
Increased irritability	5 (2)
Not feeding normally	4 (1)
Cough	4 (1)
Local infection	4 (1)
Breathing difficulty	3 (1)
Constipation	3 (1)
Vomiting	3 (1)
Rash	3 (1)
Runny nose	2 (1)
Conjunctivitis	2 (1)
Colic	2 (1)
Apnoeic episode	1 (<1)
Diarrhoea	1 (<1)
Decreased sleeping	1 (<1)
Feels hot	1 (<1)
Chest infection	1 (<1)
Not himself/herself	1 (<1)
Weight gain	1 (<1)
Others	3 (1)

INCIDENCE OF SYMPTOMS ON DIRECT QUESTIONING

The mothers of 241 babies (81%) reported one to 15 symptoms present in the previous 24 hours. Sixty nine (23%) reported one symptom, 49 (16%) reported two symptoms, 40 (13%) reported three symptoms, and 83 (28%) reported four or more symptoms. Only 57 babies (19%) were wholly free of symptoms. The number of mothers reporting symptoms when directly questioned was five times the number who expressed 'concerns' about their babies' health, and 10 times the number who thought their babies were ill.

Table 3 shows the incidence, duration, and severity of symptoms. The commonest symptoms were cold peripheries (39%), noisy breathing (30%), rash (23%) decreased sleeping (20%), runny nose (18%), and sweating (17%). Of 88 mothers reporting noisy breathing, 82 (93%) were referring to snuffles or upper airway 'mucousy' noises; three (3%) mentioned 'chesty' sounds, two (2%) wheezy noises, and one stridor. Despite the high incidence of noisy breathing, coughing was reported in only 10% of babies and breathing difficulties in 3%. Feeding disturbances were reported in 24 babies (8%). Details of the babies' intakes were obtained in 288 cases (97%). Sixteen babies (6%) had taken less fluid than normal (including five whose mothers had initially reported no feeding disturbance). Eleven had taken more than two thirds of their normal fluids and two had taken between one and two thirds. In three the actual amount taken was unknown. None had taken less than a third. In 11 cases (4%) the report of feeding disturbance referred to a change in the feeding pattern or to a reduction in the amount of solids taken, and not to a reduction in the fluid intake.

Symptoms that might be considered serious (such as decreased activity, drowsiness, apnoeic attacks, and projectile vomiting) were reported

Table 3 Incidence, severity, and duration of 28 symptoms ascertained by direct questioning of mothers of 298 babies

Symptom	Total No (%)	No (%) with moderate or severe symptoms	Duration of symptoms	
			No (%) ≤3 days	No (%) 'always present'
Cold peripheries	117 (39)	3 (1)	7 (2)	105 (35)
Noisy breathing	88 (30)	17 (6)	20 (7)	34 (11)
Rash	68 (23)	16 (5)	19 (6)	18 (6)
Decreased sleeping	61 (20)	11 (4)	23 (8)	7 (2)
Runny nose	53 (18)	11 (4)	22 (7)	1 (<1)
Sweating	51 (17)	6 (2)	7 (2)	36 (12)
Increased sleeping	45 (15)	1 (<1)	18 (6)	1 (<1)
Increased irritability	45 (15)	13 (4)	18 (6)	2 (1)
Increased crying	43 (14)	18 (6)	18 (6)	1 (<1)
Cough	42 (14)	4 (1)	16 (5)	4 (1)
Feels hot	36 (12)	22 (7)	20 (7)	9 (3)
Pallor	30 (10)	5 (2)	4 (1)	23 (8)
Not feeding normally	24 (8)	5 (2)	17 (6)	0
Vomiting	24 (8)	7 (2)	10 (3)	7 (2)
Not himself or herself	21 (7)	8 (3)	8 (3)	1 (<1)
Diarrhoea	16 (5)	4 (1)	7 (2)	2 (1)
Abnormal cry	13 (4)	4 (1)	5 (2)	3 (1)
Breathing difficulty	10 (3)	7 (2)	3 (1)	5 (2)
Less urine	9 (3)	1 (<1)	4 (1)	0
Decreased activity	7 (2)	2 (1)	4 (1)	0
Drowsy	5 (2)	1 (<1)	5 (2)	0
Jaundice	4 (1)	0	0	3 (1)
Projectile vomiting	3 (1)	1 (<1)	2 (1)	1 (<1)
Cyanotic episodes	2 (1)	0	0	2 (1)
Apnoeic episodes	2 (1)	1 (<1)	0	1 (<1)
Bile stained vomiting	0	0	0	0
Blood in stools	0	0	0	0
Convulsions	0	0	0	0

Symptoms were recorded only if they occurred within the previous 24 hours.

in 1–2% of babies. Bile stained vomiting, blood in the stools, and convulsions did not occur. Neonatal jaundice was reported in four babies.

DURATION OF SYMPTOMS

The duration of symptoms (table 3) was divided into 'recent onset' (present for three days or less), 'intermediate' (present for more than four days but less than 14 days) and 'always present' (present since birth or for more than 14 days).

SYMPTOMS OF RECENT ONSET

Although 81% of the babies had symptoms, only 38% had symptoms of recent onset (table 3). The commonest symptom, cold peripheries, was reported in 39% of babies, but was of recent onset in only 2%. Sweating was reported in 17% but was recent in only 2%. Pallor was reported in 10%, but was recent in only 1%. The symptoms with a high incidence of acute presentation were: drowsiness in 5/5 (100%), not feeding normally in 17/24 (71%), projectile vomiting in 2/3 (66%), decreased activity in 4/7 (57%), and feeling hot in 20/36 (56%).

SYMPTOMS REPORTED AS 'ALWAYS PRESENT'

A third of the symptoms were reported as always present (table 3). The commonest were cold peripheries in 35% of babies, sweating in 12%, noisy breathing in 11%, pallor in 8%, and rash in 6%. Pallor and sweating were reported as always present because mothers thought babies were pale when asleep or tired and because the babies sweated at the back of the head when feeding. Potentially serious symptoms such as cyanosis, apnoea, and breathing difficulties were occasionally reported as always present; one baby had cyanotic heart disease, two mothers gave doubtful histories, and four mothers said their babies choked with feeds and had difficulty breathing during or after such episodes. Symptoms such as passing less urine, decreased activity, not feeding normally, increased irritability, increased crying, and increased sleeping could not (by definition) be reported as present since birth. They were rarely reported as being present for longer than two weeks.

SEVERITY OF SYMPTOMS

Only 21% of the symptoms reported were graded by the mother as moderate or severe (table 3). The symptoms most likely to be graded as moderate or severe were: breathing difficulty in 7/10 (70%), feels hot in 22/36 (61%), apnoeic episodes in 1/2 (50%), and increased crying in 18/43 (43%). Those least likely to be graded as moderate or severe were: cold peripheries in 3/17 (1%), increased sleeping in 1/45 (2%), less urine in 1/9 (11%), coughing in 4/42 (10%) and sweating in 6/51 (11%).

Discussion

This paper presents accurately defined data

about the symptoms affecting 298 babies under 6 months of age seen at home. The results show that the overall incidence of symptoms in this age group is high, with many babies having several symptoms. Some of the symptoms studied were common, and had been present for many days. The mothers often considered these to be 'normal' and rarely a cause for concern.

The study population is typical of the national population for the most important social factors such as number of children in the family, single parents, and smoking, and enough babies were assessed to give good 95% confidence intervals for the incidence of symptoms. The cohort is weighted towards social class I (22%, compared with 4.5% nationally), but regression analysis taking into account the season, month of assessment, social class, mother's age, number of children in the house, parental smoking, whether the mother worked, baby's age and feeding method (breast or bottle and whether taking solids), did not show any significant effect of social class on the reporting of individual symptoms. Season and the month of assessment were the factors that influenced reporting most often, with an increased incidence of cold peripheries, decreased sleeping, runny nose, increased irritability, increased crying, cough, sweating, and rash in the winter months. The remaining factors in the analysis affected the incidence of one or two symptoms each (for example, parental smoking was related to an increased incidence of vomiting and sweating), although when comparatively small numbers of babies had the symptom (that is, less than 30 babies) it was rarely possible to show any significant effects. Further analyses are planned to explore in more detail the effect of various factors on the reporting of symptoms. If the study were to be repeated in a community where any of the factors affecting incidence of symptoms were more common (for example in a population with more smokers) the incidence of symptoms would vary in accordance with these differences. Nevertheless, the common symptoms would remain common and the rarer symptoms would remain rare. The incidence of symptoms would still be high (perhaps higher) and the comparative importance of individual symptoms as indicators of disease would be similar.

When asked whether they had any worries about their baby's health, 16% of mothers in the study expressed a concern; 8% thought that their babies were ill. When questioned specifically about the presence of individual symptoms, a third reported symptoms of recent onset. A fifth of the babies had symptoms that the mothers thought were important (graded as moderate or severe). The assessor considered that 20% of the babies were mildly or moderately ill at the time of the assessment. Thus it seems that on any day about a fifth of the babies of this age have symptoms that might be related to minor illness. Serious illnesses, however, are rare. The high incidence of symptoms and minor illness is probably a reflection of the large numbers of infective agents encountered by babies in the first few months of life, to which they must mount an immunological response.

Given that babies commonly have symptoms, the assessment of their comparative importance can be difficult. Various authors have suggested lists of serious or sinister symptoms.⁴⁻¹¹ Stanton *et al* highlighted 12 'major' symptoms that warranted medical attention the same day.⁴ These were wheezing, noisy or altered breathing, cough, diarrhoea or vomiting, unusual drowsiness, irritability or excessive crying, an altered character to the cry, being off feeds, or having difficulty feeding. The definitions used are not described and thus any comparison of their data and our own should be cautious; most of these 'major' symptoms, however, seem to be too common in babies of this age to be useful individual predictors of serious outcome. Only drowsiness and altered cry were uncommon symptoms in our study, being present in less than 5% of the babies. Reduced feeding was included in the list given by Stanton *et al*, but has been criticised as being too common in general practice to be useful.¹⁰ The results of the present study, however, suggest that a baby taking less than two thirds of the normal fluid intake is rare in the community, and no baby was taking less than one third of the normal intake. This degree of reduction in fluid intake may therefore be a useful symptom.

Some studies have used the non-specific 'presence of symptoms' as an indicator of illness in babies. Vague pointers such as 'symptoms in an infant less than 6 months old' and 'the presence of several symptoms' are, however, obviously impractical as indicators of the need for medical attention¹⁰; 41% of the babies in our study had three or more symptoms at the time of the assessment.

The incidence of symptoms in this study is higher than has been reported for control babies in previous studies.⁴⁻¹¹ This may be because of a difference in methods. Our enquiry covered more symptoms, and direct and detailed questioning about each symptom using strict definitions is likely to have increased the rate of reporting compared with the indirect and less specific methods used in previous studies.

Some specific symptoms that are known to indicate serious conditions are rare in the community. Drowsiness, decreased activity, projectile vomiting, cyanosis, and apnoea were rare. Bile stained vomiting, frank blood in the stools, and convulsions were not found in this study. These symptoms warrant an urgent medical opinion.

When taking a history, simply asking the mother what she is concerned about will not provide accurate data. The number of mothers who reported concerns about their babies was less than a fifth of the number who reported symptoms when questioned directly. Detailed and specific questions should be asked about each symptom. It is important to differentiate between symptoms that are of recent onset, or are severe, and may be related to acute illness, and those that have been present for some time, are less severe, and may be part of the normal symptom profile in the community. Pallor and sweating were often reported as being always present, and were graded as normal or mild because mothers reported healthy babies look-

ing pale when asleep and sweating when feeding. In contrast, pallor or sweating that were severe or of recent onset were rare (2% or less) and thus more likely to be signs of illness. The commonest symptom, cold peripheries, was reported as always present in 90% of the babies who had the symptom. It was rarely described as severe, and was the only symptom present in 14% of those in whom it was reported. This suggests that the symptom is normal for infants in this age group.

The degree of disturbance may need to be determined before the importance of a symptom is clear. For example, 8% of mothers reported feeding disturbances, but only 5% of babies had taken less fluids than usual and most of these had taken more than two thirds of their normal amount. None had taken less than a third. Grading of symptoms has the added advantage that it encourages careful definition of symptoms. Without specific definitions individual interpretations of symptoms can vary.¹²

There is undoubtedly a need to improve the recognition of illness in babies. The lists of 'serious' symptoms published so far have been unsatisfactory because they have not taken account of the high incidence of symptoms in the community, and the symptoms given have not been clearly defined.⁴⁻¹¹ Any assessment system used to identify babies with serious illness must have a high sensitivity to ensure that ill babies are not missed; and a high specificity to avoid increasing the workload on the primary health care team. It must take the high background incidence of symptoms into account.

This project has collected carefully defined data about the incidence, duration, and maternal impression of 28 predefined symptoms in a randomly selected group of babies seen at home during one year. The results have shown that symptoms are common in babies in the first 6 months of life, and that they cannot be interpreted without a detailed history. A few individual symptoms are rare in the community and these warrant an urgent medical opinion, but most of the rare symptoms are highly specific, and tend to be associated with particular conditions. Babies developing serious illnesses often have non-specific symptoms that would not be included in a system designed to assess the severity of a baby's illness that was based on these rare specific symptoms alone. A system of assessment based on careful grading of severity of symptoms, or on combinations of symptoms and signs, is likely to be a much more effective tool.

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Home collection of urine specimens—boric acid bottles or Dipslides?

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Abstract

Sterile mid stream specimens of urine (MSSU) were obtained from 84 children in a hospital outpatient department. All 84 children collected urine at home by one of two Dipslide methods and by collection into boric acid within 24 hours of the hospital collected MSSU. The samples collected at home were posted to the hospital. Thirty six of the Dipslides (43%) and nine of the boric acid samples (10%) were not sterile but none had a pure growth of a single organism of $>10^5$ organisms/ml. In addition, 17 of the Dipslides (20%) were returned with one or both media detached and therefore could not be relied upon to exclude urinary tract infection.

In a second part to the study, 95 urines which showed a significant growth in primary culture were also cultured after storage in boric acid. Inhibition was noted in nine samples after storage in boric acid, seven of which were in underfilled bottles. Transport of specimens in boric acid produced less contamination than Dipslides but may inhibit growth in a small number of specimens. Technical failures with Dipslides were disappointingly high.

The difficulties of home collection of urine specimens have long been appreciated and yet it remains an integral and essential part of paediatric practice. A combination of prolonged storage and transit time, often at room temperature rather than at 4°C, is one of the major confounding problems. In 1969 Porter and Brodie first used boric acid as a preservative to transport urine specimens and found little contamination despite postal delivery.¹ The results of Watson and Duerdin support this.² Modified commercial methods based on boric acid are now also available and appear to show good preservation of samples.³ The dip-inoculum transport medium technique of transporting specimens first described by Mackey and Sandys in 1965⁴ now has wide usage in its commercial form as 'Dipsides' (Difco). It has also been shown to give reliable results in the diagnosis of urinary tract infection and has gained widespread support, particularly for use in general practice,⁵⁻⁸ where it provides a method for obtaining a positive urine result within 24 hours outside the hospital setting.

In this study we have tried to establish whether Dipslides, collected by two different techniques, or urine bottles containing boric acid, provide more accurate results when used at home compared with a carefully supervised

hospital obtained mid stream specimen of urine (MSSU). Previous studies have suggested that there may be some inhibition of bacterial growth in boric acid solutions.^{1,2} In case the presence of boric acid produced false negative results, in a second part to the study we examined the effect of boric acid on the inhibition of bacterial growth.

Patients and methods

PART 1

One hundred and seven consecutive children (age range 2-18 years) attending the outpatient renal clinic were enrolled in the study. Only continent children participated. An MSSU was obtained from all children after perineal cleansing. The parents were instructed by experienced nursing staff to clean the perineum from front to back using 0.015% chlorhexidine with 0.15% cetrimide (Savlodil, ICI). Urine was stored immediately in a preservative free sterile container at 4°C before transfer to the laboratory for microscopy and culture on the same day.

Parents were instructed to clean the perineum in the same way before home urine collection. They were asked to collect the specimens on the same day as the hospital attendance. Detailed written instructions as to how to collect the samples were given to the parents in addition to a verbal explanation at the time of the clinic attendance.

The following three methods were used at home. (1) *Boric acid*. An MSSU was collected into a sterile bowl and 5 ml poured into a bottle containing boric acid (Sterilin) to yield a 1.3% solution. (2) *Dipslide 'dip'*. An MSSU was collected as above and a Dipslide was dipped into this. Excess urine was allowed to drain and the Dipslide was placed in the bottle and sealed. (3) *Dipslide 'stream'*. The Dipslide was held in the mid portion of the urinary stream, excess urine was allowed to drain and the slide was sealed in the bottle.

All children were asked to collect a boric acid sample. They were randomly allocated to collect either a Dipslide dip sample or a Dipslide stream sample in addition to this.

Parents were asked to return the specimens by first class post on the day of collection.

Laboratory methods

The length of time it took for the sample to reach the laboratory was noted.

Biochemical analysis for pH, protein, blood, ketones, nitrites, and glucose was performed using Multistix (Ames).

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An aliquot of 50 µl from each specimen was transferred into a microtitre tray using reverse pipetting. The urine was allowed to stand for 15 minutes and then examined using an inverted microscope. White blood cells, red blood cells, epithelial cells, casts, organisms, crystals, and amorphous debris were noted. Using a 1 µl standard loop (Medical Wire and Equipment Co), urine was spread on to a quarter of a 9 cm petri dish containing cysteine lactose electrolyte deficient (CLED) agar (Lab M). This was incubated at 37°C aerobically overnight. The colony counts were evaluated and organisms identified by conventional methods.

Contamination was defined as any growth on the plate or Dipslide.

PART 2

A total of 171 MSSUs were collected and were cultured immediately. A 5 ml aliquot of the remainder of each sample was put in a boric acid container and stored at room temperature. Samples were taken for culture from the boric acid specimens at 24 and 48 hours. The colony counts were compared with those of the fresh MSSUs.

The χ^2 test and the calculation of log odds ratios⁹ were used for statistical analysis of the results.

Results

The parents of 107 children agreed to take part in the study. A boric acid sample and a Dipslide, dip or stream method, was received from 100 patients, a compliance of 93.5%. In 16 of these children the initial MSSU was not sterile and they were excluded from further study. Thus there were 84 children with a sterile MSSU and both a boric acid and Dipslide sample. The results in this group of patients were further examined. There were 43 boys (age range 3–18 years, mean 8.9 years) and 41 girls (age range 2–15 years, mean 9.1 years); table 1 gives details of the diagnoses in these children.

The time taken to receive the specimens by first class post varied from one to seven days. The mean length of time to return was 1.7 days and modal length of time one day.

DIPSLIDES

Seventeen Dipslides were returned with one or both media detached (CLED, n=13; McConkey, n=2; both, n=2). These Dipslides could not be relied upon to exclude urinary tract

infection. A further 36 Dipslides were not sterile. Bacteriological details of the non-sterile Dipslides are given in table 2.

From the 84 Dipslides examined, 41 (20 girls, 21 boys) had been treated by the stream method and 38 (20 boys, 18 girls) by the dip method. The method of treatment of five (two boys and three girls) was not known. The difference between the dip and stream results in boys and girls by χ^2 just reached significance ($p=0.05$), although the relative risk of contamination as judged by the log odds ratio calculation was mean (SD) 0.91 (0.644) for boys and 1.20 (0.780) for girls, the weighted mean of these being 1.03 (0.496). A comparison of the non-sterile Dipslides in the two groups is shown in table 3.

BORIC ACID

The results of the samples collected into boric acid were examined similarly and the results tabulated in table 4.

BORIC ACID INHIBITION

From the 171 urines examined 97 were culture positive. Nine (9%) of these infected samples showed a reduced colony count after storage for 24 and 48 hours in boric acid.

In seven of the nine discrepant samples it was noted that the boric acid bottle was underfilled. The bacteriological results of the discrepant samples are given in table 5.

Table 2 Non-sterile and technically unsatisfactory Dipslides

Growth	No (%)
(1) Indeterminable (culture medium detached)	17 (20)
(2) $>10^5$ Organisms/ml	
Faecal flora	1 (1)
Two organisms	2 (2)
(3) 10^3 – 10^5 Organisms/ml	
Pure growth (any organism)	4 (5)
Faecal flora	8 (9)
Skin and faecal flora	7 (8)
Mixed skin flora	7 (8)
(4) $<10^3$ Organisms/ml	
Coliform	3 (4)
Staphylococcus epidermidis	4 (5)
Total	53 (63)

Table 3 Comparison of Dipslide methods. Results are mean (SD)

	Non-sterile Dipslides (%)		
	Dip	Stream	Unknown
Boys	13/20 (65)	9/21 (43)	2/2 (100)
Girls	15/18 (83)	12/20 (60)	2/3 (67)

Log odds ratio for boys 0.91 (0.644) and for girls 1.20 (0.780); weighted mean 1.03 (0.496); χ^2 test, $p=0.05$.

Table 1 Diagnoses of children in study

	No (%) of children
Urinary tract infection	30 (36)
Vesicoureteric reflux	
Minimal change nephrotic syndrome	6 (7)
Other glomerulonephritis	9 (11)
Haematuria (miscellaneous)	9 (11)
Chronic renal failure	8 (9)
Henoch-Schönlein syndrome	6 (7)
Proteinuria (miscellaneous)	4 (5)
Other	12 (14)
Total	84 (100)

Table 4 Non-sterile boric acid samples

Growth	No (%)
(1) $>10^5$ Organisms/ml	
Mixed faecal flora	1 (1)
(2) 10^3 – 10^5 Organisms/ml	
Coliform	1 (1)
Skin and faecal flora	2 (2)
Mixed skin flora	4 (5)
Mixed faecal flora	1 (1)
Total	9 (10)

Table 5 Anomalies in boric acid culture test (n=9)

MSSU result (organisms/ml)	24 hours in boric acid	48 hours in boric acid	Possible reason
>10 ⁵ Coliforms +candida	As MSSU	Candida only	U
>10 ⁵ Coliforms	As MSSU	10 ² Coliforms	U
<10 ⁵ Candida	As MSSU	No growth	U
>10 ⁵ Coliforms	10 ² -10 ⁵ Coliforms	<10 ¹ Coliforms	U
>10 ⁵ <i>Pseudomonas aeruginosa</i>	No growth	No growth	U+++
>10 ⁵ Coliforms	10 ³ Coliforms	10 ³ Coliforms	U
<10 ⁵ Candida	As MSSU	No growth	U
>10 ⁵ <i>Pseudomonas capacia</i>	10 ³ <i>Pseudomonas capacia</i>	10 ² <i>Pseudomonas capacia</i>	Nothing obvious
>10 ⁵ Candida	10 ⁵ Candida	10 ³ Candida	Nothing obvious

U=underfilled bottle. Bottles were underfilled if the initial specimen did not allow sufficient urine to fill the bottle.

Discussion

'I am still referred patients who have been given antibiotics without having had a urine culture taken beforehand. . . .' (White 1987).¹⁰ This is still a frequent scenario in many outpatient departments and a reliable and sufficiently robust method of collecting and transporting urine from the community to the hospital is clearly needed. Unfortunately, the results of this study show that there are problems with both Dipslides and boric acid collection. Interpretation of the results of the study depends to a large extent on the specific purpose of urine collection at home. As a screening test to identify symptomatic children who need a definitive urine culture (for example, a suprapubic sample) and to monitor children with vesico-ureteric reflux, false positive urines, in small numbers, are less of a worry than false negative urines.

An unexpected but major problem with the Dipslides was the high rate of technical failure. Altogether 20% of the Dipslides were received with one or both media detached; presumably this occurred during postal transit. They had been issued 24 hours previously and had been individually examined before issue.

If the conventional diagnostic level of >10⁵ organisms/ml is taken as defining urinary tract infection,¹¹ any child with <10⁵ organisms/ml could be considered as non-infected. On this basis, three Dipslides, plus the 17 technically unsuccessful Dipslides and one boric acid sample would need to be repeated (table 2). It is not safe to assume that a bacterial count of <10⁵ organisms/ml is necessarily benign, however, because some children with infection may have such counts.¹²⁻¹⁴ Thus if Dipslides with growths between 10³-10⁵ organisms/ml are considered as equivocal, 33 more Dipslides would need to be repeated. In this case 36 Dipslides would have equivocal growth and 17 would need repeating for technical reasons, a total of 53 (63%). Clearly, this is a far too high false positive rate for it to be a practical technique for the identification of low bacterial count infection. If this limitation is accepted, however, Dipslides are a servicable home culture technique. The number of repeat Dipslides would be very considerably reduced if they were more robust. We did not attempt to assess the 'false negative' rate for Dipslides as we felt that inhibition of growth on the culture medium, provided the specimens were collected correctly, was unlikely to occur. To do so would require a similar study to that performed on the boric acid samples in part 2 of the study.

The situation with boric acid preservation is even more complex. On face value this method of preservation is much more reliable. Using the criterion of >10⁵ organisms/ml, only one boric acid sample would need repeating. Using >10³ organisms/ml as a cut off point, a total of nine samples (10%) would need to be repeated. The second part of the study, however, showed significant inhibition of bacterial growth in nine urine samples after prolonged incubation in boric acid. Seven of these nine samples were in bottles that had been underfilled because of an initial small sample. It is reasonable to assume that the increase in boric acid concentration due to underfilling was the reason for the bacterial inhibition. Two samples were in correctly filled bottles, however, and suggest that a degree of inhibition may occur even when the correct concentration of boric acid is used. If the possibilities of urinary tract infection with a low bacterial count and the risk of reduction in bacterial count by boric acid are accepted, it is probably wise to repeat any urine transported in boric acid that has any growth in it. It would also be necessary to repeat all samples in under-filled bottles, unless they yielded >10⁵ organisms/ml. By emphasising to parents that a correct volume of urine was essential, repeat urine samples because of underfilling could be minimised. This would, thus, mean repeating more than 10% of these urines but would probably yield a very low false negative rate.

Urinary tract infections are still diagnosed too late to prevent irreversible renal damage in too many children. If we are to attempt to reduce the incidence of chronic pyelonephritis a reliable, simple diagnostic test for urinary tract infection for home use would be of great value. Dipslides, or similar home culture techniques, have great attractions and previous reports claim good agreement with MSSUs. Most of these studies have, however, been in an 'office' situation where a nurse has collected or supervised the collection of the urine sample.⁵⁻⁷ Our results suggest that these results cannot be reproduced when parents collect the urine unsupervised. In a previous study, comparing the two ways of using the Dipslide, there was a very low contamination rate using the Dipslide dip method collected under supervision and a higher contamination rate using the stream method unsupervised at home.⁷ Our results suggest that possibly there is less contamination using the stream method when both methods are compared under the same circumstances, although our results only just reach significance. The parents in our study were commit-

ted people who agreed to take part in a research protocol. Their children were accustomed to producing MSSUs and they had individual tuition from the two nurses involved. This was supported by written instructions and the urines were collected within a few hours of the clinic visit. It is likely that in routine practice the contamination rates would be even higher.

We conclude that neither method is totally satisfactory and that the method chosen should be dictated by circumstance. We suggest that to exclude a urinary tract infection in an ill child, provided that the general practitioner is prepared to examine the result, Dipslides should be used. That way, a negative result can be obtained in 24 hours, without recourse to hospital. The child should be referred to hospital for an appropriate fresh sample to be taken if the Dipslide shows a growth. The Dipslide should also be sent, to provide antibiotic sensitivities and identification of the organism. For the follow up of at risk children, we prefer boric acid. The repeat rate for Dipslides under these circumstances is unacceptably high. It would be unreasonable to expect these children to attend hospital two out of three times that they sent in a sample and this would not only cause great anxiety but also doubtless diminished compliance in the long term.

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Nocturnal enuresis in sickle cell haemoglobinopathies

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Abstract

The prevalence of nocturnal enuresis (wet at least two nights a week) was investigated in children, aged 8, who were being followed up as part of a prospective cohort study. There were 175 children with homozygous sickle cell disease, 106 with sickle cell haemoglobin C disease, and 150 controls with a normal haemoglobin genotype. In homozygous sickle cell disease, 48 boys (52%) and 31 girls (38%) were enuretic, a significantly higher prevalence than in those with sickle cell haemoglobin C disease—five boys (10%) and 11 girls (20%)—or in normal children—16 boys (22%) and 13 girls (17%). There was no significant difference between children with sickle cell haemoglobin C disease and the normal genotype. Boys with homozygous sickle cell disease were significantly more likely to be enuretic if they came from large families; there was a similar trend for girls with homozygous sickle cell disease, although it did not reach significance. Enuresis was more common in boys with homozygous sickle cell disease who had low concentrations of fetal haemoglobin and in girls with sickle cell haemoglobin C disease who had high mean corpuscular haemoglobin concentrations. Similar associations were not shown for girls with homozygous sickle cell disease or boys with sickle cell haemoglobin C disease.

Nocturnal enuresis is a common problem in general paediatric practice. The reported prevalence varies because of differences in definition, but appears to be influenced by racial or cultural factors.¹⁻⁴ Enuresis is acknowledged to be more common in children with homozygous sickle cell disease, although the reported studies have been small and usually lacked appropriate controls.⁵⁻⁷ The Jamaican cohort study of sickle cell disease has allowed the accurate documentation of enuresis in patients and controls and an assessment of associated haematological, clinical, and social risk factors.

Patients and methods

The study population consisted of the Jamaican children enrolled in a cohort study of sickle cell disease set up by the Medical Research Council Laboratories at the University of the West Indies. Neonatal cord blood screening of 100 000 consecutive normal deliveries identified all infants with major haemoglobinopathies, born at the public maternity hospital in Kingston from July 1973 to December 1981.⁸ There were 314 children with homozygous

sickle cell disease and 201 with sickle cell haemoglobin C disease. The first 125 cases with homozygous sickle cell disease were each matched with two children of the same age and sex but with a normal haemoglobin genotype, giving 250 normal controls.

Children have been reviewed regularly: at intervals of three months and at any time between when they have been ill when there have been inquiries about nocturnal enuresis. At age 8 years (± 6 months) each child was reviewed in detail and the presence or absence of enuresis noted along with other clinical, social, and anthropometric data. The present study is based on information obtained from both of these sources. For the purposes of the study enuresis was defined as being wet, regularly, at least two nights a week but for certain analyses an expanded definition of wet at least one night a month was also used.

The haematological indices examined in patients with and without enuresis were the mean of all steady state observations between 5 and 8 years of age. Routine haematological indices were measured by an electronic particle counter (Coulter ZB1 6 or Coulter S plus 4). Fetal haemoglobin was measured by the alkali denaturation method of Betke *et al.*,⁹ and the diagnosis of homozygous sickle cell disease or sickle cell haemoglobin C disease was on standard criteria.¹⁰

Prevalence rates for enuresis are quoted with 95% confidence intervals and differences between genotypes were assessed by χ^2 tests. Associations between enuresis and haematological indices were investigated by Student's *t* test; fetal haemoglobin concentrations and reticulocyte counts required logarithmic transformation before analysis to normalise skewed distributions. χ^2 tests for association and trend were used to examine the relationship between enuresis and social factors and multiple logistic regression analysis was then used to re-examine the relative contributions of family size and position in the family as these are interdependent variables. The Mann-Whitney non-parametric test was used to investigate the association of enuresis and disease severity, the latter being assessed by the total number of sick visits to clinic in the first eight years of life.

Results

The number of children, by sex and genotype, for whom reliable data were available is shown in table 1, which also shows the total number of children for whom data should have been available and hence the percentage ascertainment within each group. The discrepancy between

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Table 1 Sex, genotype, and ascertainment of cohort study children

	Homozygous sickle cell disease			Sickle cell haemoglobin C disease			Normal genotype		
	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total
Total possible sample size	109	102	211	67	65	132	88	102	190
No with reliable data	93	82	175	51	55	106	74	76	150
Ascertainment (%)	85	80	83	76	85	80	84	75	80

Table 2 Prevalence of enuresis at age 8 years

	Boys			Girls			95% Confidence interval	No (%) wet ≥ 1 night/month
	Total No	No (%) wet ≥ 2 nights/week	95% Confidence interval	Total No	No (%) wet ≥ 2 nights/week	95% Confidence interval		
Homozygous sickle cell disease	93	48 (52)	42-62	54 (58)	82	31 (38)	27-48	42 (51)
Sickle cell haemoglobin C disease	51	5 (10)	2-18	13 (25)	55	11 (20)	9-31	22 (40)
Normal genotype	74	16 (22)	13-31	21 (28)	76	13 (17)	9-25	18 (24)

Table 3 Comparison of prevalence of enuresis (wet ≥ 2 nights/week) between genotypes

	Genotypes compared		
	Homozygous sickle cell disease v normal	Homozygous sickle cell disease v sickle cell haemoglobin C disease	Sickle cell haemoglobin C disease v normal
Boys	<0.001	<0.001	0.130
Girls	0.003	0.04	0.690
Both	<0.001	<0.001	0.560

Figures indicate significance of χ^2 test (p).

the total available study population and the number of children originally enrolled in the cohort study is accounted for by those children who died, those who emigrated or were lost to follow up, and those who had not yet reached 8 years of age at the time of the study. The age distribution of children within each genotype at the time of the eight year review was comparable with a mean (range) for homozygous sickle cell disease of 8.0 (7.5-8.5), sickle cell haemoglobin C disease of 8.1 (7.9-8.5), and normal genotype 8.1 (7.5-8.5).

Prevalence rates for enuresis by genotype and sex are shown in table 2. Children with homozygous sickle cell disease were significantly more likely to be enuretic than either those with sickle cell haemoglobin C disease or those with a normal genotype ($p < 0.001$), there being no statistical difference between the latter two genotypes (table 3). None of the differences between the sexes reached significance.

SOCIAL FACTORS

When data for boys and girls were analysed together, children with homozygous sickle cell disease were significantly more likely to be

enuretic if they came from larger families ($p = 0.003$, table 4) but children from single and dual parent families had similar rates of enuresis. Later position in the family was significantly associated with enuresis for children with homozygous sickle cell disease ($p = 0.005$, table 4) but multiple logistic regression analysis showed that this could be largely accounted for by the effect of family size. The data in table 4 are compiled defining enuresis as wet at least two nights a week, although the same associations with family size ($p = 0.001$) and position in family ($p = 0.03$) are true for the expanded definition of wet at least once a month. Again the association with position within the family could be accounted for by the effect of family size.

When analysed separately by sex, there was a significant positive association for boys with homozygous sickle cell disease between family size and enuresis defined either as wet at least two nights a week ($p = 0.002$) or wet at least one night a month ($p = 0.008$), but there was no association between enuresis and position in the family. For girls with homozygous sickle cell disease there was a trend, which did not reach significance, for enuresis to be more common in children from larger families when defined as wet at least twice a week but no association was seen with position in the family. For the expanded definition of wet at least once a month, enuresis was significantly more common both with increasing family size ($p = 0.02$) and with later position in the family ($p = 0.03$). Multiple logistic regression analysis showed these associations to be interdependent, neither one reaching significance when corrected for the effect of the other. No association was found between enuresis and three assess-

Table 4 Effect of family size and position in family on prevalence of enuresis among children with homozygous sickle cell disease

	No of children					Position in family				
	1	2	3	4	5+	1st	2nd	3rd	4th	5th+
Total No subjects	18	31	39	34	38	54	36	25	23	22
No (%) enuretic	4 (22)	9 (29)	20 (51)	18 (53)	22 (58)	18 (33)	17 (47)	17 (68)	9 (39)	12 (54)
$p = 0.03; \chi^2$ test for association $p = 0.003; \chi^2$ test for trend						$p = 0.05; \chi^2$ test for association $p = 0.005; \chi^2$ test for trend				

Table 5 Association of enuresis (wet ≥ 2 nights/week) with steady state haematological indices for children with homozygous sickle cell disease

Variable	Mean (SD) enuretic	Mean (SD) non-enuretic	t	p Value
<i>Boys</i>				
Haemoglobin (g/l)	76.0 (9.3)	79.0 (10.6)	-1.60	0.1
Fetal haemoglobin*	0.79 (0.28) 5.2%†	0.91 (0.28) 7.1%†	-2.03	0.05
Mean corpuscular haemoglobin concentration (g/l)	342 (26)	343 (16)	-0.34	0.7
Reticulocytes*	1.07 (0.12) 10.7%†	1.07 (0.12) 10.7%†	+0.15	0.9
<i>Girls</i>				
Haemoglobin (g/l)	82.0 (10.3)	80.0 (10.5)	+0.92	0.4
Fetal haemoglobin*	0.87 (0.22) 6.4%†	0.87 (0.28) 6.4%†	+0.14	0.9
Mean corpuscular haemoglobin concentration (g/l)	345 (16)	344 (17)	+0.24	0.8
Reticulocytes*	1.09 (0.11) 11.3%†	1.07 (0.13) 10.7%†	+0.84	0.4

*Indices expressed transformed by $\log_{10}$ (variable+1).

†Denotes means expressed in original units.

Table 6 Association of enuresis (wet ≥ 2 nights/week) with steady state haematological indices for children with sickle cell haemoglobin C disease

Variable	Mean (SD) enuretic	Mean (SD) non-enuretic	t	p Value
<i>Boys</i>				
Haemoglobin (g/l)	106.0 (5.9)	104.0 (7.9)	+0.46	0.6
Fetal haemoglobin*	0.30 (0.06) 2.0%†	0.36 (0.17) 2.3%†	-0.77	0.4
Mean corpuscular haemoglobin concentration (g/l)	356 (15)	355 (13)	+0.24	0.8
Reticulocytes*	0.65 (0.12) 3.5%†	0.70 (0.14) 4.0%†	-0.68	0.5
<i>Girls</i>				
Haemoglobin (g/l)	112.0 (8.0)	108.0 (7.7)	+1.60	0.2
Fetal haemoglobin*	0.45 (0.19) 2.8%†	0.48 (0.22) 3.0%†	-0.40	0.7
Mean corpuscular haemoglobin concentration (g/l)	363 (8)	353 (13)	+2.38	0.02
Reticulocytes*	0.76 (0.21) 4.7%†	0.69 (0.14) 3.9%†	+1.33	0.2

*Indices expressed transformed by $\log_{10}$ (variable+1).

†Denotes means expressed in original units.

ments of socioeconomic status: the provision of running water inside the home or in the 'yard'; the presence of a flush, rather than a 'pit' toilet, and the provision of mains electricity in the home. Moreover there was no significant difference between the prevalence of enuresis for those children from families with all of the amenities and those with none.

For children with sickle cell haemoglobin C disease there were no trends or significant associations between enuresis and any of the social factors. For children of normal genotype the only significant finding was that girls were more likely to be enuretic if the family had a 'pit' rather than a flush toilet ($p=0.02$, for enuresis defined as wet at least twice a week). It should be noted, however, that for both of these genotypes the number of enuretic children in the analyses was small and this may have contributed to the lack of significant trends or associations.

HAEMATOLOGICAL FACTORS

Children with homozygous sickle cell disease (table 5)

When data for boys and girls were analysed together there were no significant associations but concentrations of haemoglobin A₂ tended to be higher in the enuretic than the non-enuretic group ($p=0.05$). When analysed separately enuretic boys tended to have lower concentrations of fetal haemoglobin than non-enuretics ($p=0.05$) but for girls the concentrations were similar for the two groups. No other associations or consistent trends were demonstrated.

Children with sickle cell haemoglobin C disease (table 6)

For boys and girls analysed together, mean

corpuscular haemoglobin concentration tended to be higher in the enuretic than the non-enuretic group ($p=0.05$). When analysed separately enuretic girls had significantly higher values for mean corpuscular haemoglobin concentration ($p=0.02$) than non-enuretic but for boys the values were comparable for the two groups.

There was no association with α thalassaemia status for either genotype.

DISEASE SEVERITY

The number of visits for illness to the clinic in the first eight years of life, used as a measure of disease severity, was significantly greater for enuretic than non-enuretic boys with homozygous sickle cell disease ($p=0.03$) but for girls a greater number was found in the non-enuretic than the enuretic group, although the difference did not reach significance.

Discussion

The present study confirms the previously suggested association between homozygous sickle cell disease and nocturnal enuresis, the prevalence at age 8 years being at least twice that found in control subjects of normal haemoglobin genotype. A similar association could not be shown for sickle cell haemoglobin C disease, prevalence in this genotype being similar to that in controls. The data do not, unfortunately, allow accurate differentiation of primary and secondary enuresis, but it is our impression that most children with homozygous sickle cell disease, who were still wet at 8 years of age, had primary enuresis.

Previous studies have suggested that the higher prevalence of enuresis in children with homozygous sickle cell disease is due to their

poor urinary concentrating ability,^{4 5} which results from sickling within and destruction of the vasa recti countercurrent system of the renal medulla.¹¹ This is thought to produce larger diurnal and nocturnal urinary volumes and hence delayed attainment of nocturnal urinary continence. The present study casts doubt on the simplicity of this hypothesis. If this were the only factor responsible for the higher prevalence of enuresis in children with homozygous sickle cell disease then one might expect a clear association between enuresis and haematological or clinical indices thought to reflect disease severity. Moreover, a higher prevalence of enuresis might have been expected in children with sickle cell haemoglobin C disease in whom medullary vascular damage also occurs.¹¹

The present study has shown a weak association between enuresis and low concentrations of fetal haemoglobin for boys with homozygous sickle cell disease and a stronger association between enuresis and high mean corpuscular haemoglobin concentration values for girls with sickle cell haemoglobin C disease. Both of these haematological indices might be expected to enhance sickling within the renal medullary vasculature and produce more severe damage. The significance of these findings is difficult to assess, however, given the absence of similar associations in girls with homozygous sickle cell disease and boys with sickle cell haemoglobin C disease and the failure to show a higher prevalence of enuresis in girls with sickle cell haemoglobin C disease than in normal controls. It is also difficult to interpret the finding that enuresis was associated with a greater number of visits because of illness to the clinic and possibly, therefore, a more severe clinical course for boys with homozygous sickle cell disease when the opposite was found for girls with homozygous sickle cell disease.

Our results, therefore, have not excluded an effect of renal medullary damage and high urinary volumes in the aetiology of enuresis in sickle cell disease but suggest that additional factors must be involved.

Enuresis in children with homozygous sickle cell disease showed, for boys, a significant positive association and, for girls, a clear trend with increasing family size in the present study. This has been reported previously for normal children, convincingly in a recent² and less convincingly in an older¹² cohort study from Britain. Other workers have reported similar trends that did not reach significance.^{13 14} This suggests that factors contributing to enuresis in normal children are also important in children with homozygous sickle cell disease. The lack of association between enuresis and the three measures of socioeconomic status in the present study might seem contradictory as most previous studies have shown at least a trend,¹⁴ and usually a significant association,^{2 12 13} between lower social class and enuresis. This can probably be explained by the social homogeneity of the cohort children's families, however, and the relative unreliability of social amenities in predicting social status in Jamaica, as a family in

the country without running water or electricity may have a better standard of living than a family in Kingston who have both. The aetiological factors for enuresis in normal children and those with homozygous sickle cell disease, therefore, are probably similar but factors specific to the homozygous sickle cell genotype must contribute to the prevalence, which is more than twice as high as in the normal children. The present study has not enabled these to be identified and further research will be needed to clarify the situation.

It is interesting that the prevalence of nocturnal enuresis in the controls with normal genotype was high compared with previously published normal population data. It is higher than that reported for Afro-American children in Baltimore,³ who themselves were more likely to be enuretic at 8 years than their white counterparts. These data, however, were not corrected for socioeconomic status, which is generally thought to influence the prevalence of enuresis in normal children. More recently, enuresis has been reported to be more common among Afro-Caribbean than white children in Britain and this association was shown to be independent of social class.² Normal population data are not available for Jamaican children but preliminary results of a survey in Jamaican basic schools suggest that the controls of normal genotype in the cohort study are representative of the general population (DRJ Readett, unpublished observations).

In summary, this study has shown a definite association between nocturnal enuresis and homozygous sickle cell disease in children in Jamaica and has accurately documented the prevalence at 8 years of age. It has not provided an explanation for this association but has questioned the simplicity of existing theories and highlighted the need for further study.

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Persistent diarrhoea: clinical efficacy and nutrient absorption with a rice based diet

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Abstract

Twenty six infant boys, aged 4 to 18 months, suffering from persistent diarrhoea and 25 age matched healthy controls without diarrhoea were given a diet based on rice powder, egg white, glucose, and soya oil. The clinical efficacy of the diet was studied and a 72 hour metabolic balance study was done. Twenty one patients recovered from diarrhoea within seven days. Median coefficients of absorption of nutrients in persistent diarrhoea patients were 68.0% (range 28.0 to 92.0) for total energy, 60.0% (range 21.0 to 97.0) for fat, 53.0% (range 12.0 to 82.0) for nitrogen, and 81.0% (range 23.0 to 97.0) for carbohydrates. The corresponding values among the control subjects were 90.0% (range 76.0 to 99.0), 95.0% (range 71.0 to 99.0), 70.0% (range 10.0 to 95.0), and 93.0% (range 85.0 to 98.0) respectively. Absorption of all macronutrients in the control subjects was on average significantly higher than in the patients. Nutrient absorption is substantially reduced in persistent diarrhoea and a rice based diet is clinically effective in most patients.

Patients and methods

About 70 000 patients annually attend the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) treatment centre; about 300 of these patients have persistent diarrhoea. Twenty six boys, aged 4 to 18 months, who qualified for the study were selected consecutively. Inclusion criteria were: non-bloody diarrhoea lasting for more than 14 days and liquid or watery stools with a frequency of four per day or more. Exclusion criteria were: isolation of *Vibrio cholerae*, *Salmonella* spp, or *Shigella* spp from the stools, systemic infections, kwashiorkor, and exclusive breast feeding. The 25 healthy controls of comparable age were selected from the children who had visited ICDDR,B for diarrhoea at least four months earlier and had no history of diarrhoea within the previous two months. This study was approved by the ICDDR,B ethical review committee. Informed written consent was obtained from the parents of the subjects. On the day of admission, the patients were rehydrated, with an intravenous polyelectrolyte solution containing sodium 133 mmol/l, potassium 13 mmol/l, chloride 98 mmol/l, and bicarbonate (as acetate) 48 mmol/l.

Persistent diarrhoea is frequent in children from deprived communities. Its cause is still largely unknown. Though there is no general agreement, persistent diarrhoea has been defined as an episode of apparently acute diarrhoea that, however, lasts for more than 14 days.¹ Intestinal pathogens are rarely isolated from the stools of patients with persistent diarrhoea.² The management remains problematical,³ and very sophisticated and special procedures have been used.⁴ There are only a limited number of studies on malabsorption of nutrients in acute diarrhoea⁵ due to specific enteropathogens⁶ and none in persistent diarrhoea. In persistent diarrhoea, malabsorption of nutrients has been attributed to loss of brush border enzymes,⁷ small intestinal bacterial overgrowth,⁸ derangement of bile acid metabolism,⁹ mucosal injury associated with cows' milk protein sensitive enteropathy,¹⁰ and severe protein energy malnutrition¹¹ with reduced brush border and pancreatic enzymes.¹²⁻¹³ Symptomatic management of persistent diarrhoea with different diets has been partially successful.²⁻⁴⁻¹⁴ Yet proper choice of the ingredients of a successful diet needs an assessment of intestinal absorption capacity. A clinical trial and a metabolic balance study was undertaken to test the effectiveness of a simple diet and to examine the importance of malabsorption in persistent diarrhoea.

BASELINE INVESTIGATIONS

The following data were collected: measurement of food and fluid intake, stool, urine, and vomit every eight hours. Blood electrolytes, white cell count, routine urine analysis, stool microscopic examination for *Giardia lamblia* and cryptosporidium were done on admission. Stools were cultured for *V. cholerae*, *Shigella* spp, *Salmonella* spp, enterotoxigenic *Escherichia coli*, and *Campylobacter jejuni* by standard microbiological techniques. For detection of rotavirus an enzyme linked immunoabsorbent assay (ELISA) method was used. Stool pH was measured with a pH meter and glucose was estimated by a glucose oxidase method.¹⁵ On admission body weight, length, and mid upper arm circumference were taken by a trained nutritionist. Subsequently, the children were weighed daily at the same hour (9-10 am). A metabolic balance (Ohaus) with a precision of 1 g was used to measure the body weight. Length was measured by a locally made length board with a precision of 1 mm and mid upper arm circumference by a TALC (Teaching Aid at Low Cost) tape with a precision of 2 mm. Nutritional state was calculated as percent of the 50th centile National Center for Health Statistics standard.¹⁶ For estimation of intake of breast

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Table 1 Composition of study diet

	Weight (g)	mmol/l
Rice powder	30	—
Egg white	50	—
Soya bean oil	20	—
Glucose	25	139
Potassium chloride	1	13
Sodium chloride	1	17
Magnesium chloride	0.5	5
Calcium chloride	1	9
Water (ml)	935	
Cooked volume (ml)	1000	
Energy (MJ)	1.67	
Osmolality (mmol/kg)	280	

milk, the patients were weighed before and after each breast feeding.

STUDY DIET

A liquid diet was prepared with rice powder, egg white, soya oil, glucose, salt, and water. It contained 0.17 MJ/100 ml with 8% energy from protein (table 1). The diet was prepared as follows. The ingredients were collected and measured as required with a balance. The whites of two duck eggs were separated, weighed, and then mixed with rice powder, glucose, and soya oil and taken in about a litre of water and boiled for about five minutes. The final volume was made up with additional water and then salts and minerals were added. The cost of the diet was US\$ 0.25 for one litre. Hourly feeds were given freely. Breast feeding on demand was encouraged. The diet was given for at least seven days. If there was evidence of clinical deterioration with increased diarrhoea a comminuted chicken based diet was given. Recovery was defined as a change of stool consistency from liquid to soft. Success with the study diet was defined as recovery within seven days.

BALANCE STUDY

The balance study was done as described by Molla *et al.*⁶ It was initiated 24 hours after patients and control children started taking the study diet. Charcoal was given as a marker at the start of the balance period and 72 hours later. Collection of stool and urine was done after the appearance of the first marker and until that of the second one. Five ml of acetic acid were put in the stool collecting pot to reduce bacterial growth and fermentation. After weighing the homogenised 72 hour stool samples, aliquots were analysed for total fat by Vande Kamer's method,¹⁷ nitrogen by the

micro-Kjeldahl method,¹⁸ and total energy by adiabatic bomb calorimetry (Gallenkamp); carbohydrate was calculated by subtracting energy for fat and nitrogen from the total energy. The coefficient of intestinal absorption was calculated as: $[(\text{Intake}-\text{loss})/\text{intake}] \times 100$.

STATISTICAL PROCEDURES

After entering data in a microcomputer, they were analysed using SPSS/pc+ software. Significance was assumed at the probability level of 5%. Only age, length, and mid upper arm circumference were normally distributed. Therefore the Mann-Whitney U test was used for comparison between groups. Wilcoxon's matched pair signed test was applied when subjects were used as their own controls.

Results

All 26 study children had liquid stools on admission. A total of six stool pathogens were isolated from stools of four patients. *Campylobacter* (n=1), enterotoxigenic *E coli* (n=3), and rotavirus (n=2). Seven days after the start of the diet, 21 (81%) of the children had soft stools and were considered as having recovered. Nine of these patients (43%) had already achieved recovery after three days. The remaining five children (19%) failed to recover within seven days and were given a diet based on comminuted chicken. Their daily stool weights and frequencies are given in table 2. Table 3 compares the main characteristics of the five children in whom treatment failed with those of the children who recovered. There were no differences in age, anthropometric indices, or duration of diarrhoea before admission. The median stool weights on days 1 and 5 were much higher in the children who failed to recover, however ($p<0.01$ and $p<0.002$ respectively), and so were the median coefficients of absorption for total energy ($p<0.001$). All five who failed to recover were breast fed. Two of them developed bronchopneumonia and one developed urinary tract infection; all three responded well to antibiotics. All five recovered from their prolonged diarrhoea after a period ranging from nine to 39 days.

BALANCE STUDY

The general characteristics of patients and controls are given in table 4. Nutritional state of the controls was significantly better. Table 5 compares the dietary intake of patients and controls. The average total energy (MJ/kg/day) and nutrient intakes (g/kg/day) from the study diet were comparable between the groups but there was a significantly higher intake of breast milk among the patients. The balance, that is, intake-loss of energy and nutrients, however, indicated no significant differences between the two groups except for fat (table 6). More control children than patients were weaned, but the difference was not significant. Among the patients, malabsorption was most prominent for nitrogen and least so for carbohydrate (table 7), but some patients had coefficients of absorption

Table 2 Median (range) daily average stool weight and stool frequency of the patients during the first five days on the study diet

Days	Stool weight (g/kg/day)	Stool frequency (No/day)
1	98 (31-329)	14 (4-40)
2	86 (11-255)	11 (2-24)
3	84 (13-357)	9 (1-35)
4	71 (3-310)	8 (1-29) [†]
5	65 (6-398) [*]	7 (2-42) [*]

^{*} $p<0.002$ and [†] $p<0.01$ when compared with day 1 (Wilcoxon's matched pair signed test).

Table 3 Main features of the five children who did not improve on rice based diet and those who recovered

	Case 1	Case 2	Case 3	Case 4	Case 5	Median (range) for children who recovered
Age (months)	11	7	8	8	9	8 (5-17)
Weight for age (% median NCHS)	58	90	69	64	48	67 (49-85)
Weight for height (% median NCHS)	75	90	79	79	65	82 (66-90)
Duration of diarrhoea before admission (days)	15	26	25	45	20	17 (14-60)
Stool weight (g/kg/day):						
Day 1	237	55	266	150	330	92 (31-203)
Day 5	240	398	217	123	204	33 (6-135)
Time taken for recovery (days)	22	9	11	39	15	4 (2-7)
Energy intake from breast milk (MJ/kg/day)	0.17	0.18	0.27	0.18	0.20	0.15 (0.0-0.24)
Coefficient of absorption:						
Nitrogen	-10.0	52.0	23.0	3.0	13.0	59 (-122-82)
Fat	26.0	71.0	38.0	37.0	43.0	61 (21-97)
Carbohydrate	94.0	55.0	23.0	73.0	32.0	85 (35-97)
Complications	—	—	Urinary tract infection	Lower respiratory tract infection, oedema	Lower respiratory tract infection, sepsis, oedema	
Drugs	SXT, metronidazole		SXT, gentamicin	Ampicillin, gentamicin	SXT, ampicillin, gentamicin	

NCHS, National Center for Health Statistics.
SXT, Sulphamethoxazole-trimethoprim.

Table 4 Comparison of general characteristics between children with persistent diarrhoea and their controls. Results are median (range)

	Patients (n=26)	Controls (n=25)	p Value*
Age (months)	8.5 (5-17)	10 (5-18)	0.14
Weight (kg)	6 (4.3-8.4)	8 (6.7-11.7)	0.001
Length (cm)	66.6 (56.0-75.0)	70.5 (60.5-79.5)	0.002
Weight for age (% median NCHS)	66.7 (47-90)	84.7 (68-109)	0.001
Weight for length (% median NCHS)	80.8 (64-108)	98.6 (81-117)	0.001
Mid upper arm circumference (cm)	11.5 (9-13.7)	13.3 (11.5-14.9)	0.001

*Mann-Whitney U test.

NCHS, National Center for Health Statistics.

Table 5 Comparison of nutrient intake between children with persistent diarrhoea and their controls. Results are median (range)

	Patients (n=26)	Controls (n=25)	p Value*
Energy total (kcal/kg/day)	0.40 (0.23-0.65)	0.33 (0.20-0.53)	0.0007
Energy from diet alone	0.29 (0.16-0.45)	0.26 (0.13-0.53)	0.60
Energy from breast milk (MJ/kg/day):			
All children	0.18 (0.0-0.27)	0.4 (0.0-0.16)	0.0002
Breast fed children only	0.18 (0.01-0.27) (n=22)	0.07 (0.01-0.16) (n=16)	0.0001
Nitrogen (g/kg/day)	0.33 (0.22-0.54)	0.29 (0.2-0.8)	0.01†
Fat (g/kg/day)	4.9 (3-7.9)	4 (2.4-6.3)	0.0014†
Carbohydrate (g/kg/day)	10.5 (5.5-17.5)	8.7 (5.5-18.8)	0.005†

*Mann-Whitney U test.

†Intake from study diet was not different.

comparable with those of the control subjects. In the controls, median coefficient of absorption of nitrogen was only 70%; it was very low in two patients: 10% and 37%, respectively. While the coefficients of energy and nutrients absorption

Table 6 Comparison of energy and nutrient balances between patients and controls. Results are median (range)

	Patients (n=26)	Controls (n=25)	p Value
Energy balance (MJ/kg/day)	0.23 (0.08-0.54)	0.29 (0.18-0.50)	0.37
Fat balance (g/kg/day)	2.9 (0.8-6.4)	3.7 (2.3-6.1)	0.03*
Nitrogen balance (g/kg/day)	0.17 (-0.3-0.38)	0.19 (0.03-0.42)	0.30
Carbohydrate balance (g/kg/day)	8.0 (3.0-17.0)	7.7 (5.1-17.7)	0.88
Intake of dietary energy (MJ/kg/day)	0.28 (0.15-0.45)	0.26 (0.13-0.53)	0.67
Non-breast fed/total children	4/26	9/25	0.30†
No of feeds at the breast/day‡	7 (3-12)	4 (2-9)	0.05*

*Mann-Whitney U test; † χ^2 test.

‡Mean of three consecutive days during balance period.

Table 7 Comparison of the coefficients of absorption (%) between patients and controls. Results are median (range)

Macronutrients	Patients (n=26)	Controls (n=25)	p Value*
Total energy	68 (28-92)	90 (76-99)	0.001
Nitrogen	53 (-122-82)	70 (10-95)	0.001
Fat	60 (21-97)	95 (71-99)	0.001
Carbohydrate	81 (23-98)	93 (85-98)	0.001

*Mann-Whitney U test.

overlapped between the two groups, the median values were significantly different.

Discussion

In rural Bangladesh persistent diarrhoea, especially when associated with malnutrition, is considered as one of the most important causes of death in 1 to 4 year old children (V Fauveau, M Yunus, K Zaman, *et al*, unpublished observations). Despite the severity of the disease and absence of definite outlines for management, most of our patients have been successfully treated with a simple rice based diet. The

patients were severely ill, most of them were malnourished, and they had prolonged diarrhoea with high purging rates and gross malabsorption. Whether malnutrition was a cause or effect of persistent diarrhoea is not clear. Despite the high median purging rate (98 g/kg/day) during the first 24 hours of admission, only half of the patients needed intravenous rehydration. This was consistent with the rapid response to the diet. The rapid recovery of 21 out of 26 patients compares well with the recovery of only three children out of 26 with a usual milk based diet reported previously,² the more so because the diet is an inexpensive one and easily made locally. However, the present study did not address specific issues like comparisons with established treatment regimens, including use of intravenous fluids, and cost comparison. Both average stool weight and frequency diminished considerably and quickly during the first five days on the study diet. In the five children who did not improve with the study diet, stool weights increased and stool frequency remained high, and three among them had signs of systemic infection. It is not known to what extent the infections were responsible for the prolongation of the illness. These patients were not more malnourished than the other patients; clearly malnutrition was not correlated with treatment failure. The therapeutic diet had a low energy density (0.17 MJ/100 ml) and the children were not used to its taste. The low energy density of the diet was due to its composition, which was about the half strength of a previously used diet with a success in about 50% of patients.² This might explain the low average energy intake in both groups. Most of the patients were breast fed; this is the normal practice in this community. The intake of breast milk in our patients was of similar magnitude to that reported in children with acute diarrhoea.^{19,20} A recent study in this country has shown that breast feeding reduces mortality among malnourished children. The much higher intake of breast milk by the patients is striking. The patients suckled more frequently than the controls. It is the higher volume of breast milk that led to a significantly higher median energy intake in the patients than in the control children. Yet the higher intake was offset by severe malabsorption and the energy balance in patients and controls was similar. Patients had on average severe malabsorption of energy, nitrogen, and fat. The absorption of carbohydrate was relatively higher, which might explain the success of our diet. Yet some of our patients had a normal coefficient of absorption while some of the control children cannot be considered as having a normal intestinal absorption. The latter has been found in another study from this country.²¹ As shown in acute diarrhoea, the carbohydrate absorption was higher than that of nitrogen and fat.⁶ Despite a low average absorption and energy balance the response to the diet was highly satisfactory. After the first week of treatment, the patients who improved were put on a diet with an energy density of 0.33 MJ/100 ml. They showed a rapid weight gain whereas

during the first week of treatment their weight remained constant or decreased. The gross malabsorption in most cases of prolonged diarrhoea might explain the association of this disease with malnutrition and its high fatality rate. The diet we have used seems to be of real value as any moderately well equipped hospital should be able to prepare it, and it could be prepared at home. The search for a still more simple diet and for ways to prevent persistent diarrhoea must be continued.

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Anorexia nervosa complicating inflammatory bowel disease

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Abstract

Two cases of inflammatory bowel disease, occurring in adolescence and complicated by anorexia nervosa, are presented. The management of the bowel disease with corticosteroids appeared to precipitate the eating disorder in one case whereas covert withdrawal of steroid treatment led to life threatening complications of inflammatory bowel disease in the other. The difficulties of managing two serious conditions, each ideally treated in a specialist centre, are discussed and the dangers of treating adolescents with shape modifying drugs are highlighted.

Inflammatory bowel disease is now increasingly recognised in children and adolescents, although it is still underdiagnosed.^{1 2} The incidence of anorexia nervosa is unknown, but in cases with prepubertal onset, the ratio of male to female sufferers is much higher than for older age groups and the diagnosis is often missed.³ We present two cases of childhood anorexia nervosa, one in a boy who subsequently developed ulcerative colitis and the other in a girl whose Crohn's disease was complicated by the eating disorder. In both these cases corticosteroid treatment played a pivotal part and the management of one condition was profoundly and adversely affected by the other.

Case reports

CASE 1

A 14 year old Iranian boy was admitted to his local hospital with a short history of abdominal pain and diarrhoea. Ulcerative colitis was diagnosed by sigmoidoscopy and biopsy and he was treated with oral prednisolone, sulphasalazine being contraindicated because of glucose 6-phosphate dehydrogenase deficiency. He was referred for further assessment because of continued symptoms, the diagnosis being confirmed at colonoscopy where moderate, predominantly distal disease was seen with biopsy specimens showing classical ulcerative colitis. He was stabilised on a mixture of oral and rectal steroids.

At referral his height lay on the 90th centile with weight just below the 50th centile (49 kg). Examination showed him to be in early puberty. During follow up it became apparent that he was steadily losing weight and he was referred for psychiatric assessment. It transpired that he had been eating abnormally since the age of 12 after remarks made by girls at school about his weight. Two months before the onset of his abdominal symptoms he had apparently weighed

63 kg on his home scales and had determined to lose weight. He competed with his sister in this, developing a regime of intensive daily exercise and keeping a diary of food intake. He became obsessed by food, feeling that he had lost control if he did eat. He indulged with his sister in days of binge eating, after which she would induce vomiting and he would punish himself by increasing his exercise regime. He had undoubted disturbance of body image, feeling that his shoulders were becoming larger and more manly in the face of an emaciated appearance and the loss of more than 30% of his ideal body weight.

During the following months he became resentful of his steroid treatment as he felt it disturbed the shape of his face (he particularly wanted his cheekbones to be prominent) and he secretly stopped it. His colitis relapsed quickly and he was readmitted as an emergency with severe abdominal pain and bloody diarrhoea. His haemoglobin concentration had dropped to 80 g/l and colonoscopy now showed a severe pancolitis. Despite high dose intravenous steroids he deteriorated, developing toxic megacolon that required emergency subtotal colectomy with ileostomy. Postoperatively he was concerned about the energy in his dextrose-saline infusion. His weight had dropped to a nadir of 32 kg, a 50% fall in 10 months.

His subsequent progress has been complicated by ileostomy dysfunction, secondary sodium depletion, and by several episodes of subacute obstruction. Attempts to admit him to two adolescent psychiatric units were refused because of the complexity of his medical problems. Planned transfer to a third unit was postponed because of recurrent abdominal pain. Attempts to establish a strict behavioural regime on the general paediatric ward were unsuccessful in increasing his weight as he was adept at feigning compliance while actually avoiding food and covertly exercising.

His subsequent psychiatric management has been conducted largely as an outpatient, both at this hospital and by referral to a department of adolescent psychiatry. He has attended with his parents and sister for sessions of family therapy, which have provided evidence of a considerable disturbance of family relationships. On this regime, although he physically improved and gained weight, he withdrew from the family to the extent of refusing to talk to his parents, although continuing to live at home.

Despite his continuing problems at home he has begun to show improvement in terms of weight gain (reaching 45 kg) and has also demonstrated less disturbance of body image.

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His management has been complicated by multiple admissions with abdominal pain due to recurrent small bowel obstruction. Because of this and an intractable offensive discharge from his mucous fistula he has recently undergone excision of the rectum with ileoanal reanastomosis after creation of an ileal pouch.

CASE 2

A previously well girl presented at 11.7 years to her local hospital with a three month history of abdominal pain, diarrhoea, and weight loss. Examination showed anal fissures with skin tags and Crohn's colitis was diagnosed on barium enema, sigmoidoscopy, and biopsy. She was treated initially with an exclusion diet, sulphasalazine, and oral prednisolone. She improved symptomatically until her medication was stopped by her parents who had heard of other relatives who had gained weight unacceptably on steroid treatment. Her parents took her to a succession of hypnotherapists, homoeopaths, and other alternative practitioners. During this six month period her general health remained poor and she was unable to return to school, and she received home tuition. At age 12.9 years she frankly relapsed with bloody diarrhoea and hypoproteinaemic oedema. Her parents returned her for review and she was recommenced on prednisolone and sulphasalazine before being referred for further assessment. Colonoscopy and biopsy confirmed patchy Crohn's colitis and barium studies showed no evidence of small bowel disease. Her prednisolone was reduced.

Two months later she was brought to hospital by her grandparents, her parents being unconcerned, because of loss of weight. Her weight had fallen from 40 kg (above 10th centile) to 32.5 kg despite good symptom control and no rise of her disease indices. She had become increasingly fussy about her diet and was eating separately from the rest of the family.

She was readmitted for assessment where it became clear that she was avoiding food and secretly exercising. She had a considerable disturbance of body image (figure) and, after formal psychiatric assessment, a diagnosis of anorexia nervosa was made. She admitted that she had become concerned about her weight when she was started on steroids and felt that she had lost control of her own body shape. At

school she had been teased and called 'hamster-cheeks'.

Despite an apparent intake of 5.02 MJ/day her weight fell to 29 kg and her parents eventually agreed to her admission to an adolescent psychiatric inpatient unit. Three units were unable to admit her, two expressing concerns that they would be unable to manage her Crohn's disease (she was currently asymptomatic). Attempts to establish a behavioural regime on the general paediatric ward were partially successful and eventually she was discharged while further attempts were made to find a suitable adolescent unit.

Her disease has subsequently remained quiescent, allowing reduction to low dose alternate day prednisolone. She required admission to her local hospital on one occasion because of food refusal and is currently receiving outpatient treatment at a local family consultation centre. Her weight has improved substantially to 38 kg and she displays a more normal body image.

Discussion

Anorexia and weight loss may occur purely as a consequence of inflammatory bowel disease, without any disturbance of body image or other features to suggest a primary disturbance of eating behaviour.² Exacerbation by eating of the abdominal pain due to inflammatory bowel disease may lead to avoidance of a normal diet and consequent weight loss.⁴ The diagnosis of Crohn's disease may be delayed if anorexia and weight loss, without fear of weight gain or body image disturbance, are ascribed to anorexia nervosa.⁵⁻⁷ There have been several reports of inflammatory bowel disease presenting as anorexia nervosa,⁵⁻⁸ or of anorexia nervosa complicating known inflammatory bowel disease.⁹ All reported cases have been female and in general the diagnosis of anorexia nervosa has been based on the criteria of Dally and Sargent.¹⁰ These criteria are: (i) that the subject is less than 35 years old; (ii) a refusal to eat; (iii) a more than 10% weight loss; (iv) an absence of schizophrenia, severe depression, or organic illness; and (v) more than three months amenorrhoea.

These features omit the characteristic psychopathological features of intense fear of weight gain and body image disturbance that are now considered essential for diagnosis.¹¹ In addition, there is an erroneous assumption in the older literature that the condition only occurs in young females. Only two of these reported cases would fulfil modern diagnostic criteria for anorexia nervosa.^{6,9}

Both our cases show the difficulties in the management of potentially life threatening conditions in what is essentially the wrong setting. The treatment of anorexia nervosa is ideally carried out in a specialist centre with staff experienced in dealing with the unique demands and food avoidance stratagems of these patients. Both our patients were managed in a busy general paediatric ward and were able to circumvent behavioural approaches with relative ease. They would both apparently



The girl (case 2), who was a talented cartoonist, produced this picture of herself (weight 32 kg) and her mother (weight >50 kg).

comply with dietary regimes while actually taking a fraction of their documented intake. The boy was frequently reported in the nursing notes to be 'cheerful and eating well'. The girl underwent precise (and much resented) dietary assessment, showing an actual intake of only 1.25 MJ/day instead of the 5.02 MJ she was thought to be receiving. Attempted referral of both patients to appropriate psychiatric units was refused because of concern about the management of organic disease where there was no resident paediatric cover. The boy in particular was able to use his symptoms to forestall an arranged transfer and both would have been able to use their abdominal symptoms to ensure transfer back to the paediatric unit when they became resentful of the management of their eating disorder.

The features and management of each of these two conditions may clearly affect the other. Two cases of Crohn's disease and bulimia nervosa have been described in which corticosteroid treatment affected the role of the eating disorder.¹² Similarly, in both of our cases, the role of corticosteroid treatment was central. The boy stopped his treatment because of perceived changes in body shape and suffered life threatening consequences. Anorexia nervosa appears to have been precipitated in the girl by the rapid weight gain secondary to high dose steroid treatment. The use of corticosteroids is frequently unavoidable in inflammatory bowel disease, but the risks involved in such treatment at an age when a preoccupation with body shape is common should be clearly understood. The use of alternative management strategies such as elemental diet for small bowel disease should be considered, and patients should be fully counselled about the effects of steroids before they are started. Patients should be followed up regularly and specifically questioned about eating problems. Suspicion of abnormal eating behaviour or unexplained weight loss warrants early formal psychiatric assessment and admission for observation.

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Commentary

Childhood onset anorexia nervosa is often a difficult condition to diagnose and it is frequently overlooked. In one study, the average time from onset to diagnosis was nine months.¹ The main reasons for the frequent delay in diagnosis are the child's denial and secretiveness. Thus the pathognomonic symptoms such as fear of fat and distorted body image are commonly denied, and other common features such as *determined* food avoidance, preoccupation with weight and calories, self induced vomiting, exercise and laxative abuse are usually disguised. Anorexia nervosa may all the more easily be overlooked when it complicates inflammatory bowel disease.

In the two patients described by Mallett and Murch, the diagnosis was made on the basis of overt symptoms. In the first case, the boy had a two year history of binge eating, excessive exercising, preoccupation with food intake, weight and body shape, all superimposed upon weight loss. In the second case, the girl had a far shorter history of weight loss, abnormal eating behaviour, and of distorted body image.

How is a diagnosis of anorexia nervosa made in a child with inflammatory bowel disease whose symptoms are far less overt? Firstly, the paediatrician must always be aware of the possibility of a concomitant psychiatric disorder in any child with serious illness. The incidence in such circumstances may be as high as 25%. The regular use of a multiaxial diagnostic scheme such as the International Classification of Diseases² avoids the either/or dichotomy and instead encourages due consideration being given to medical, psychiatric, developmental, intellectual, and social status. Secondly, the paediatrician should have a high index of suspicion when assessing a child with poorly explained weight loss. Certainly the diagnosis should never be excluded on the basis of negative answers to questions about concerns regarding food, weight, and appearance. Thirdly, the diagnosis can almost always be made while the discussion focuses on what would constitute a satisfactory weight, and how much energy should be consumed each day. At this point, children with anorexia nervosa almost always become distressed, argumentative, and negativistic in just the same way as do children whose school phobia has presented with recurrent abdominal pain when told they should now return to school. Finally, if doubt remains, careful observation in hospital will reveal characteristic abnormal eating behaviour and a strong element of secretiveness.

Early diagnosis of anorexia nervosa complicating inflammatory bowel disease is imperative and not only is the condition much harder to treat when treatment is delayed, but as Mallett and Murch have demonstrated it can cause major and even life threatening complications.

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Langerhans cell histiocytosis: the case for conservative treatment

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Abstract

Fifty eight children with Langerhans cell histiocytosis who were referred to this hospital between 1980 and 1987 were studied. Fourteen had single system disease, and 44 had multisystem disease, of whom 22 had vital organ dysfunction. A conservative approach to treatment was adopted, and when systemic treatment was indicated a short course of prednisolone was used first. Eight of the patients with single system disease required no treatment, while six received local treatment alone. Eight of the patients with multisystem disease did not require systemic treatment, 17 were given prednisolone alone, and 19 were given cytotoxic drugs. Of the 14 with single system disease 13 had no long term after effects. Eight of the patients with multisystem disease died, 24 had long term after effects, and 12 had none. Outcome was related to age and Lahey score.

These results compare favourably with other series in which more aggressive approaches were used, and support our conservative approach to treatment.

Langerhans cell histiocytosis is a rare disease and all the previous large studies have included patients presenting over several decades,¹ patients seen at several centres,² or both.³ There is a wide variation in classification and treatment of patients among centres, and supportive treatments (such as antibiotics) change with time and tend to improve results. Historically, Langerhans cell histiocytosis was regarded as malignant and treated with increasingly aggressive regimens of chemotherapy. It is now generally considered to be reactive and flow cytometric studies support this view.⁴

Langerhans cell histiocytosis presents in different ways, and there is, as yet, no uniformly accepted classification system of extent of disease. This, combined with its rarity, means that few adequate comparative treatment studies have been carried out. At this hospital a conservative approach has been adopted since 1980. Single system bony disease is treated where possible with curettage or injection of steroids into the lesion. Multisystem disease is treated only if there is evidence of constitutional upset (fever, pain, immobility), failure to thrive or worsening disease in vital organs. Pulsed high dose prednisolone is given first, in a dose of 2 mg/kg/day for a month, and then tailed off over a two month period.⁵ Cytotoxic drugs, initially vinblastine or vincristine, and more recently etoposide, are used as second line agents.

The aim of this study was to look at the outcome of patients with Langerhans cell histiocytosis treated at this hospital over a relatively short time, and to see how their morbidity and mortality compared with those of published studies in which more aggressive and prolonged chemotherapy regimens were used.

Patients and methods

All patients with Langerhans cell histiocytosis who were referred to the haematology and oncology department at this hospital between 1980 and 1987 were studied. These dates were chosen as all children presenting during this period had been seen and assessed by one clinician (VB).

The age of the child at referral, sex, and the systems affected were recorded. Patients were allotted a score at initial diagnosis, using the system devised by Lahey in 1962² and modified in 1975.⁶ The type and number of courses of treatment, if any, were noted. Outcome was assessed both by allocating a score and by adding up the total number of courses of systemic treatment up to a maximum of six. Where steroids were given continuously, each three month period of treatment was regarded as a separate course. Morbidity was also assessed.

Results were analysed by regression of ordinal (dependent) data using GLIM (Royal Statistical Society).

Results

Between 1980 and 1987, 60 children with Langerhans cell histiocytosis were referred, 58 of whom had the diagnosis made by histological examination of the biopsy specimen and two who had single system disease of bone and in whom the diagnosis was made on the radiological appearance. The histopathological diagnoses were made before strict pathological guidelines were published by the Histiocyte Society, but the necessary material was not available to make definite retrospective diagnoses according to these criteria.⁷ Sufficient follow up information was available for 58 children.

The age range at presentation was 0 to 15 years. The distribution was skewed with a median of one year. There were 40 boys and 18 girls; 50 patients were white Europeans, six were Asians, one was oriental, and one was negroid.

EXTENT OF DISEASE

Fourteen children had single system disease; in

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13 the disease was affecting bone and in one skin. Of the 44 with multisystem disease, 22 had 'vital organ dysfunction' (lung, liver, or haemopoietic systems) as defined by Lahey.⁶

LAHEY SCORE

The number of patients with each Lahey score and the association between Lahey score and age is shown in table 1. Children aged 2 years or under had higher Lahey scores than those aged over 2 years at diagnosis.

TREATMENT

Of the patients with single system disease, eight had no treatment apart from a diagnostic biopsy. One was given radiotherapy, four had operations (excision of a skin plaque (n=1), curettage of bone lesions (n=2), and laminectomy (n=1)), and one had steroid injected into the lesion.

Of the 44 patients with multisystem disease, five had no treatment, one had topical mustine alone to the skin, and two had radiotherapy alone. Of 36 children treated with prednisolone, 21 also required cytotoxic drugs.

OUTCOME

Of the 14 children with single system disease, one who had radiotherapy in 1981 now has a minor periorbital deformity, but 13 have no after effects.

Of the 44 with multisystem disease, eight (two girls and six boys) died (18%); all the children who died had been less than 2 years old at presentation, had developed vital organ dysfunction, and died within two years of pre-

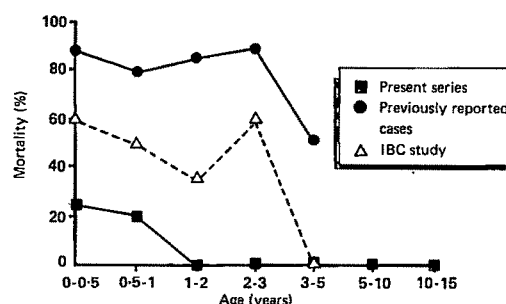


Figure 1 Age related mortality in the present series compared with the two groups reported by Lahey.² IBC = Iowa, Baltimore, and Cincinnati.

sentation. The male:female ratio among the deaths corresponded roughly to the ratio in the whole group.

Table 1 shows the outcome and age at presentation, and table 2 is a life table of survival after diagnosis. Figure 1 shows the age related mortality in our series compared with those published in Lahey's first paper.² The Lahey series may, however, include patients who would not be considered to have Langerhans cell histiocytosis using present diagnostic criteria. Comparison of actuarial rather than crude survival rates would have been preferable but this information is not given in other series. Table 3 shows the percentage surviving in the present series, and the Dutch-Austrian-German histiocytosis X (DAL-HX)⁸ and the AEIOP studies,⁹ divided according to the presence or absence of vital organ dysfunction. These show that our mortality is no worse than in these other European trials in which more aggressive and prolonged treatment was used. Toogood *et al* reported the results of aggressive chemotherapy in 25 children, of whom 13 would have been defined by us as having multisystem disease, including five with vital organ dysfunction.¹⁰ Five children (38%) died of overwhelming sepsis, including two in whom only bone and gingiva were affected, and who would have been unlikely to be given systemic treatment at our centre.

Twelve patients with multisystem disease (including six of the eight who were not given systemic treatment) had no long term after effects. Four had orthopaedic abnormalities alone, nine had endocrine dysfunction alone, one had hearing deficit alone, one had liver fibrosis alone, and nine had more than one of the above. Sixteen patients (36%) had diabetes

Table 1 Lahey score, mortality, and age at presentation

Age at presentation (years)	No. of patients	Average Lahey score	No who died
0	7	3.4	2
1	22	4.3	5
2	7	2.6	0
3	6	2.3	0
4	2	1.5	0
5	0		
6	1	2.0	0
7	2	2.0	0
8	1	1.0	0
9	5	3.0	0
10	1	1.0	0
11	1	1.0	0
12	2	1.0	0
13	0		
14	0		
15	1	3.0	0

Table 2 Life table for patients with multisystem Langerhans cell histiocytosis

Interval since diagnosis (years)	No of deaths	No of patients alive at start of interval	Estimated probability of death	Estimated probability of survival	Percentage of survivors at the end of each year
0	6	44	0.1364	0.8636	100
1	2	38	0.0526	0.9474	86
2	0	34	0	1	82
3	0	33			
4	0	29			
5	0	24			
6	0	18			
7	0	9			
8	0	3			

Table 3 Two year survival in the present study, compared with the DAL-HX 83 study,⁸ and the AEIOP study⁹

	No (%) survivors at two years
Present study:	
With organ dysfunction	14/22 (64)
With no organ dysfunction	22/22 (100)
Dutch-Austrian-German histiocytosis X (DAL-HX) study ⁸ :	
With organ dysfunction	7/11 (64)
With no organ dysfunction	26/26 (100)
AEIOP study ⁹ :	
With organ dysfunction	5/10 (50)
With no organ dysfunction	Numbers not given (90)

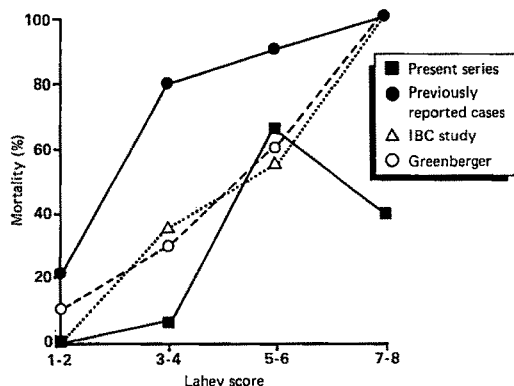


Figure 2 Mortality and maximum Lahey score in the present series compared with the two groups reported by Lahey² (previously reported cases and IBC study) and the series reported by Greenberger *et al.*³ IBC=Iowa, Baltimore, and Cincinnati.

insipidus, which in 11 patients was associated with other disease related morbidity. In all cases chronic morbidity was the result of the disease rather than of its treatment.

The maximum Lahey score was highly significantly related to both outcome score ($p < 0.001$) and number of courses of treatment ($p < 0.0001$). There was no significant association between Lahey score at presentation and either of these outcome measures. Figure 2 shows the mortality and maximum Lahey score compared with those in previously reported series.

Discussion

A child who dies of Langerhans cell histiocytosis usually does so within two years of diagnosis, either from the disease or complications of treatment.¹¹ Of the 36 patients with multisystem disease in our series diagnosed more than two years before the analysis, seven have died. Of the eight more recently diagnosed patients still at risk, one has died; this gives an overall mortality of 14%, or 36% of patients with organ dysfunction. All eight children died of progressive Langerhans cell histiocytosis, none died of the complications of treatment. Survival for the whole group of 86% compares favourably with series of children treated more aggressively with combination chemotherapy for much longer periods (table 3, figs 1 and 2). All authors agree that children under 2 years of age who present with multisystem soft tissue disease and vital organ dysfunction as defined by Lahey have the highest mortality. The aim of treatment in these patients is to reduce this mortality, but there is no evidence that this goal is being achieved by more aggressive chemotherapy.¹⁰ The change in concept of the disease to a 'reactive condition' rather than cancer suggests the need for immune modulation rather than intensification of chemotherapy in the future.

The survival of all our patients with single system disease is not unusual, but it is noteworthy that this has been achieved with minimal intervention—presumably an advantage to patients.

Morbidity in our series was confined to patients with multisystem disease, apart from

one child with single system periorbital bony disease who was left with a minor facial deformity. Twenty four of 36 survivors had some after effects, and this is comparable with other studies such as those of Lahey² and Sims,¹ in which more aggressive continuous treatment was used. The rate of diabetes insipidus in our group (36% of those with multisystem disease) was similar to the 35% in Sims's study¹ and four of 13 (31%) in the series reported by Toogood *et al.*¹⁰ but is in contrast to the 18% in the AEIOP study, and 4% in the DAL-HX study. This may reflect referral bias in our patients, or a higher percentage of patients in our series with extensive disease and higher Lahey scores. Alternatively, it may be a true consequence of our less intensive treatment. Further studies are needed, however, to determine whether aggressive or maintenance treatment prevents the development of diabetes insipidus.

There is no suggestion to date that aggressive chemotherapy prevents other long term after effects. It may, however, be both myelosuppressive and immunosuppressive, and previous regimens of chemotherapy were associated with at least a 5% risk of inducing malignancy in the long term.³

Comparing morbidity and mortality among series is hampered by the lack of uniformly accepted methods for evaluation of the extent of disease, and of the response to treatment. A working group of the Histiocyte Society is currently studying this question. With a 'common language' the way would be open for both useful comparisons and international studies, preferably randomised. Until that time we suggest that those caring for patients with Langerhans cell histiocytosis should consider a conservative, rather than an aggressive, approach. Nevertheless, it is critical that initial referral should be to a major centre with a commitment to clinical and basic research in Langerhans cell histiocytosis. Centralisation of tissue and data should advance the day when the mechanism of the disease is understood and rational treatment designed. 'Shared care' arrangements can and should be made when long distance referral is necessary.

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Partial splenectomy in homozygous β thalassaemia

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Abstract

Partial splenectomy was performed on 30 patients with homozygous β thalassaemia to reduce blood requirements and to avoid the risk of overwhelming postsplenectomy infections; 24 patients had thalassaemia major and six thalassaemia intermedia. Five patients received a high transfusion regimen before and after surgery and 25 a lower one. Follow up after surgery ranged from one to four years. Partial splenectomy improved the long term haematological state in the six patients with thalassaemia intermedia. Recurrence of hypersplenism occurred in nine of the 24 patients with thalassaemia major, however, and complete splenectomy was required. Serum IgM concentrations were not significantly modified by surgery. The mean (SD) residual spleen after surgery was 4.45 (2.36) cm measured by scintigraphy. No severe infections occurred after surgery; however, most patients were routinely treated with phenoxymethylpenicillin and the protective effect of the remaining spleen could not be exactly determined. Because of the possibility of recurrence of hypersplenism, routine partial splenectomy when splenectomy is needed in thalassaemia major is not advised, except in children under 5 years whose risk of overwhelming postsplenectomy infection is greatest.

Hypersplenism is a very common complication in homozygous β thalassaemia. In regularly transfused patients it is suspected before the increased blood consumption and is sometimes associated with thrombocytopenia or leucopenia, or both. A high blood transfusion regimen usually delays this complication,¹ though it doesn't always suppress it. Splenectomy allows for the reduction of transfusional blood requirements thus reducing iron overload.² However, this operation exposes patients, who are mainly under 5 years of age (but also older children and even adults), to the risk of overwhelming postsplenectomy infections.^{3,4} The severity of these infections has led to the search for alternative surgical techniques to replace total splenectomy so that blood requirements are reduced but the splenic contribution to the host defence against infections is preserved.

We report our experience with 30 thalassaemic patients who underwent one of these alternative techniques, partial splenectomy.

Patients and methods

Thirty patients affected with homozygous β

thalassaemia were included in the study; 24 had thalassaemia major and six thalassaemia intermedia. The diagnosis of thalassaemia major and intermedia was based on transfusion requirements.⁵ The patients' mean (SD) age was 7.9 (3.7) years (range 3-19 years) at the time of the partial splenectomy. Twenty five patients received a low transfusion regimen and five received a high transfusion regimen (table 1).

In all patients about nine tenths of the total hypertrophied splenic mass was ablated at operation. The size of the remaining portion was approximately half that of a normal spleen. The mean haemoglobin concentration was determined in each patient before and after partial splenectomy.

In order to determine the reduction of hypersplenism we monitored the postsplenectomy blood requirements, splenic blood flow,⁶ and platelet count. Blood consumption was evaluated in thalassaemia major patients by calculating the transfusion quotient.¹ Transfusion quotient is the ratio of the annual observed blood consumption to the expected one for the transfusion scheme. Hypersplenism raises the

Table 1 Mean haemoglobin concentrations, transfusion regimen, and outcome after partial splenectomy in 24 patients with thalassaemia major

Case No	Mean haemoglobin concentration (g/l)	
	During year before splenectomy	During follow up after splenectomy
<i>High transfusion regimen/no recurrence of hypersplenism</i>		
1	100	122
2	115	118
3	115	128
4	105	116
5	121	123
Mean (SD)	111 (8)	121 (4)
<i>Low transfusion regimen/no recurrence of hypersplenism</i>		
6	80	94
7	46	57
8	70	73
9	67	73
10	72	55
11	93	63
12	84	79
13	67	63
14	96	71
15	70	68
Mean (SD)	74 (14)	69 (11)
<i>Low transfusion regimen/recurrence of hypersplenism</i>		
16	57	77
17	82	84
18	90	84
19	67	95
20	76	75
21	60	70
22	50	71
23	60	80
24	64	86
Mean (SD)	67 (12)	80 (8)

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transfusion quotient above 1.5 to 2. All these values were determined before and after surgery. This ratio cannot be used in thalassaemia intermedia patients, therefore their annual blood consumption in relation to the mean haemoglobin concentration before transfusion was studied.

To try to assess preoperative hypersplenism, splenic blood flow was also measured in eight of our patients. This isotopic study, involving labelled platelets, evaluates the splenic blood volume per minute and relates it to the total blood volume. Results range from 3 to 6% in normal subjects and rises when hypersplenism occurs. Splenic blood flow after surgery was measured in 10 subjects.

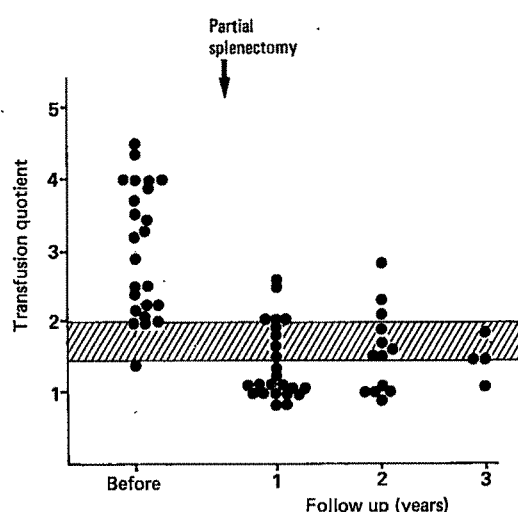


Figure 1 Transfusion quotient before and after partial splenectomy in 24 patients with thalassaemia major. The shaded area indicates the range of transfusion quotient above which is consistent with hypersplenism.

Table 2 Transfusion quotients in nine patients with thalassaemia major who had partial correction and/or recurrence of hypersplenism after partial splenectomy (indicated by transfusion quotient ≥ 2)

Case No	Before surgery	After 1 year	After 2 years	After 3 years
16	3.1	1.5	2.7	
17	3.5	1.2	2.2	
18	4.0	1.3	2.3*	1.5
19	2.3	1.0	2.0	
20	4.3	2.0		
21	3.8	2.0		
22	4.0	2.6		
23	3.4	2.0		
24	2.5	2.5		

The case numbers correspond to those in table 1.

*Total splenectomy performed.

Table 3 Results of partial splenectomy in six patients with thalassaemia intermedia

Case No	Year before partial splenectomy		Follow up period		
	Mean annual haemoglobin (g/l)	No of transfusions during year	Years of follow up	Mean haemoglobin (g/l)*	No of transfusions
1	62	1	2	100 (1) 80 (2)	1 0
2	50	12	4	80 (1) 65 (2) 70 (3) 70 (4)	0 0 0 3†
3	50	6	1	90	0
4	64	4	1.5	84	0
5	45	12	2	81 (1) 86 (2)	0 0
6	60	12	2	73 (1) 73 (2)	0 0

*Numbers in parentheses indicate year concentration measured.

†Patient died from cardiac failure.

Platelet counts were regularly made on all patients after surgery.

Spleen host defence against infections was determined by: (a) a clinical survey of infections; (b) measurements (by scintigraphy) of residual splenic mass in 25 patients (splenic size being considered as an indicator of splenic macrophage function); and (c) variations of serum IgM concentrations.

All patients were vaccinated preoperatively with a pneumococcal polysaccharide vaccine and most of the patients were postoperatively given prophylactic phenoxymethylpenicillin according to the proposal by Colonna and Ardjoun.⁷

Follow up after partial splenectomy was one year in 13 patients, two years in 12, three years in four, and four years in one.

Results

Surgery was uneventful in all patients.

The changes in the transfusion quotient in the 24 thalassaemia major patients is shown in fig 1. The mean (SD) value for the transfusion quotient before partial splenectomy was 3.07 (0.90) and one year after 1.42 (0.50). In five patients, however, the transfusion quotient after surgery was ≥ 2 , which meant that there had been insufficient correction or a recurrence of the hypersplenism. Two years after surgery four additional patients presented with a recurrence of hypersplenism (tables 1 and 2). Partial correction or relapse, or both, always occurred in patients on a low transfusion regimen. Among patients on a low transfusion regimen the mean haemoglobin concentrations before and after surgery did not differ between those with and without a recurrence of hypersplenism (table 1).

All six patients with thalassaemia intermedia had reduced blood requirements (table 3). The mean (SD) haemoglobin concentration before surgery was 55.2 (7.8) g/l—with transfusion frequency ranging from one to 12 transfusions/year—and after surgery 81.2 (9.8) g/l. All patients except one are no longer being transfused after splenectomy. One patient with thalassaemia intermedia who needed three transfusions four years after surgery (reduced from 12 before) died from cardiac failure.

Mean (SD) splenic blood flow measured preoperatively was 9.5 (5.0)% and measured 15 days after splenectomy 4.2 (3.4)%. The associa-

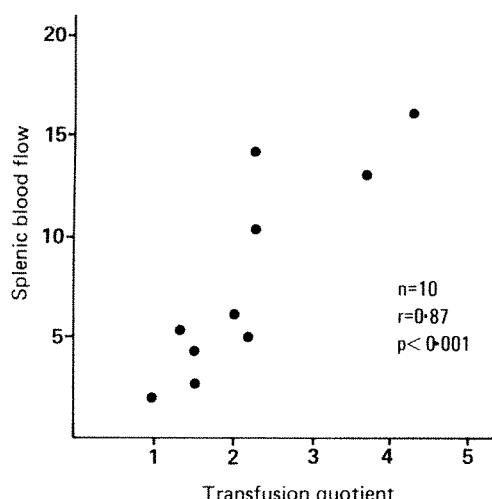


Figure 2 Correlation between splenic blood flow and transfusion quotient preoperatively.

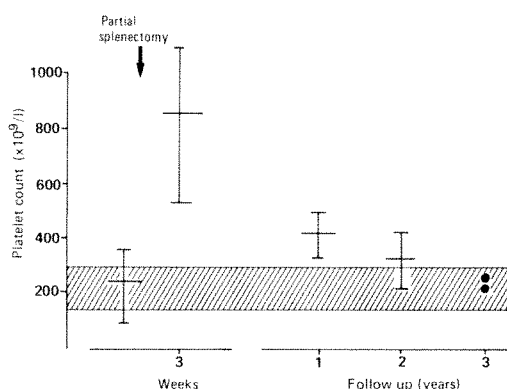


Figure 3 Mean (SD) platelet count before and after partial splenectomy in 30 patients with thalassaemia. The shaded area indicates the normal range.

tion between transfusion quotient and splenic blood flow was strong, as shown in fig 2 ($r=0.87$; $p<0.001$).

Figure 3 illustrates the effects on platelet counts: before surgery nine patients had thrombocytopenia (platelets under $150 \times 10^9/l$) and the mean (SD) value for the 30 patients was $206 (103) \times 10^9/l$. In the third week after surgery thrombocytosis occurred (mean (SD) platelet count $831 (268) \times 10^9/l$, $n=30$) with no complications resulting. One year after surgery the mean (SD) platelet count had fallen to $411 (109) \times 10^9/l$ ($n=21$), and after two years it fell within the normal range: $319 (107) \times 10^9/l$ ($n=11$).

No severe infection was noted after surgery. The mean (SD) postoperative residual splenic size, as determined by scintigraphy, was $4.45 (2.36)$ cm. Serum IgM concentrations were not significantly modified by surgery. The mean (SD) concentration before partial splenectomy was $16.4 (7.8)$ g/l. It rose to $19.6 (13.2)$ g/l three weeks later and remained at $17.8 (9.4)$ g/l one year later.

Discussion

In thalassaemic patients hypersplenism is most

probably due to hypertrophy of the reticulo-endothelial system. It is suspected before splenomegaly, leucopenia and/or thrombocytopenia, and chiefly by an increase in transfusion requirement to maintain a normal haemoglobin concentration. This results in an increased iron overload in hypertransfused patients. Despite chelation treatment, iron balance is positive in most of these subjects, exposing them to the morbidity and mortality of haemosiderosis: hepatic and endocrine complications and cardiac failure. Splenectomy reduces blood consumption and with desferrioxamine treatment allows iron balance to be achieved.² Splenectomy is beneficial against transfusional haemosiderosis even if it suppresses a reticuloendothelial iron store.¹ Splenectomy also exposes the patient to an important risk of infection: overwhelming postsplenectomy infections are frequent in children under 5 years but also found in adults.³ These infections mainly occur during the first months after surgery, but some severe infections have been observed many years after surgery. The most commonly involved organisms are *Streptococcus pneumoniae* (about 50% of cases), *Haemophilus influenzae*, and *Neisseria meningitidis*.^{3, 8}

The spleen has several immunological functions: it may phagocytose blood borne antigens in the presence of low concentrations of antibodies, participate in opsonisation, and generate specific antibodies; it maintains the integrity of the alternative complement pathway and has an 'immune memory'.^{9, 10} To preserve these functions, alternative techniques to total splenectomy have been proposed in thalassaemia patients: partial splenic embolisation,¹¹ partial vascular disconnection of the spleen,¹² or partial splenectomy.¹³ Hypersplenism is reduced in many cases, but not consistently: relapses are sometimes observed after an excellent initial result. The total number of patients treated with each of these techniques is low, however, and in some cases follow up periods have been short. No definite conclusions can be drawn from our results regarding the absence of severe infection after surgery for several reasons. Most patients followed up in Algeria were routinely given phenoxymethylpenicillin to protect them against infections, but the number of patients who had a splenectomy was low and therefore conclusions cannot be drawn on the anti-infection protective effect of the residual spleen. Serum IgM concentrations did not decrease after splenectomy, however.

Concerning the correction of hypersplenism in terms of blood requirements, we noted a positive effect of partial splenectomy in most of the patients during the follow up period of the study. The influence of the blood transfusion regimen is important because no relapse occurred in patients on a high transfusion regimen; on the contrary a partial correction or relapse was observed in almost half of the patients on the low transfusion regimen. This finding discourages us from routinely performing partial splenectomy when splenectomy seems needed in patients on a low transfusion regimen, and no definite conclusions can be drawn in patients on a high transfusion regimen, but further studies

would be useful. We suggest that partial splenectomy be limited to children under 5 years, whose risk of severe infection is greatest; this leaves the option of total splenectomy should relapse occur.

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Influence of inspiratory flow rate upon the effect of a Turbuhaler

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Abstract

The effect of a new breath actuated dry powder inhaler, the Turbuhaler*, was found to be reduced at inhalations slower than 28 l/minute. This flow rate could be generated by virtually all children aged ≥ 6 years, by 42 of 57 children < 6 years (74%), and by six of 15 preschool children with acute wheeze (40%).

Many children with asthma cannot use a pressurised aerosol correctly and therefore gain little benefit from inhalation treatment with this device. In such cases dry powder inhalers may be a valuable treatment alternative. However, powder inhalers require a certain minimum inspiratory flow rate from the patient to work effectively.^{1,2} This limits the use of powder inhalers in children, whose inspiratory flow rate varies, both with age and expiratory pulmonary function.

Dry powder inhalers are designed in different ways and vary substantially in resistance to air flow. It is important, therefore, for physicians prescribing inhalation treatment for children to know in detail the peak inspiratory flow rate (PIFR) that various age groups can generate through an inhaler as well as the lowest inspiratory flow rate at which the inhaler will work effectively.

We conducted the present studies to answer these questions with regard to a new multidose powder inhaler, terbutaline Turbuhaler (Astra), which delivers pure freeze dried drug without any carrier substance or additives.

Patients and methods

STUDY 1—MODES OF INHALATION

Ten boys and four girls, aged 7 to 15 years (mean 10 years), participated in the study. All suffered from chronic or episodic wheeze associated with an increase in forced expiratory volume in one second (FEV_1) of at least 20% after one puff of terbutaline. All received regular inhaled treatment with β_2 stimulants, 12 received inhaled corticosteroids, and three slow release theophylline. The study was approved by the ethics committee of Northern Jutland, and informed consent was obtained from all children and their parents.

The design was that of a randomised, controlled double blind, double dummy crossover study. Each child participated on two separate occasions at the same time of the day. One day

terbutaline was inhaled as fast as possible and another day at inspiratory flow rates around 22 l/minute. When the results from these two days had been analysed the children participated for another two days, one at inspiratory flow rates around 30 l/minute and one at inspiratory flow rates around 10 l/minute (randomised sequence). On each study day the children always inhaled from two different Turbuhalers, one containing terbutaline and one placebo. Different flow rates were used with the two inhalers to ensure the blinding of the study.

On all four days the children inhaled as deeply as possible from residual volume and the breath was held for 10 seconds after the inhalation.

To evaluate if maximum bronchodilation had been achieved by the inhaler treatment the children inhaled four puffs of terbutaline (1 mg) from a pressurised aerosol with a Nebuhaler (Astra) at the end of each study day. Pulmonary functions were repeated 30 minutes after this treatment.

Before each visit, treatment with inhaled corticosteroids was stopped for 48 hours and treatment with β_2 agonists and theophylline for 12 hours.

To be included in the study, pretreatment FEV_1 had to be $\leq 70\%$ of the predicted value or show a total increase $\geq 35\%$ on each study day. Furthermore, a study on each child was only performed if the baseline FEV_1 was within 15% of its value on the first study day, and if this was not the case the child was asked to make a further visit on another day.

The patients inhaled through a Turbuhaler in series with a pneumotachygraph. A total of 0.25 mg terbutaline was given on each study day and the children wore a nose clip during inhalation. Throughout the inhalation the children could see the variation with time of both inspiratory flow rate and inhaled volume on the screen of an oscilloscope. This was used as a teaching aid so that all children, after some practising in the morning, were able to make reproducible, standardised inhalations at a fixed inspiratory flow rate. Inspiratory flow rates and volume were recorded for analysis.

Pulmonary function was measured before, and at 30 minutes and at one, two, three, four, and five hours after each inhaler treatment. The measurements were performed on a Vitalograph with a pulmonary function analyser and the bronchodilator response was assessed by measuring changes in FEV_1 , forced vital capacity (FVC), forced midexpiratory flow rate (FMEF), and peak expiratory flow rate (PEFR). Both absolute values and percentage

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*The Turbuhaler is known as the Turbuhaler in the United Kingdom.

change were evaluated. The best of three measurements was studied.

STUDY 2—PIFR IN NORMAL CHILDREN

To evaluate the maximum inspiratory flow rates that various age groups of children can generate through the Turbuhaler, 265 children aged between 3.5 and 15 years were taught to inhale as quickly and deeply as possible through the inhaler in series with the pneumotachygraph. The flow and volume time curves were recorded and the best of three measurements was analysed. In addition, PEFR was measured on a Mini Wright peak flow meter, and FEV₁ and FVC on a Vitalograph (best out of three). These measurements were done in all children in a kindergarten and a small state school who were able to cooperate.

STUDY 3—ACUTE ASTHMA

Thirty four asthmatic children aged between 4 and 13 years (mean 7.4 years) were studied as described in study 2 during an episode of acute wheeze at the outpatient clinic.

STATISTICS

Friedman's test was used to evaluate any overall difference between treatments. Both absolute values, percentage change, and area under the time/pulmonary function curves (AUC₀₋₃₀₀) were evaluated. If significant effects for treatment or time were found the results were analysed by Wilcoxon's rank sum test. A *p* value of <0.05 was considered significant.

Results

MODES OF INHALATION

All 14 children completed the study. No period or carry over effects were found and no side effects observed.

Mean PIFR was 60 l/minute (range 47–72) during fast inhalations and 31 (range 28–33), 22 (range 20–24), and 13 (range 12–15) l/minute during the three other treatments. The corre-

sponding mean inhaled volumes were 1.9, 1.8, 1.4, and 1.5 l, respectively; 1.4 l being significantly lower than 1.8 and 1.9 l (*p*<0.05).

The FEV₁ as a percentage of the predicted value before and after the four Turbuhaler treatments is shown in fig 1. There was no significant difference between the initial FEV₁ on the four days of treatment. The FEV₁ before treatment varied from 40% to 82% (mean 58%) of the predicted value.

All inhalations resulted in a significant increase in FEV₁, which lasted throughout the study period for inhalations at 60 and 31 l/minute and for four and three hours for inhalations at 22 and 13 l/minute, respectively. There was no difference between the response after inhalation at 60 l/minute and inhalations at 31 l/minute. The improvement after both these treatments was significantly greater than that after inhalations at 22 l/minute (*p*<0.01). Furthermore, reducing the inspiratory flow rate to 13 l/minute diminished bronchodilation even further (*p*<0.01 compared with inhalations at 22 l/minute), so that AUC₀₋₃₀₀ was only 33% of the AUC₀₋₃₀₀ after flow rates around 60 l/minute.

After all four modes of inhalation the Nebuhaler treatments given at the end of the day resulted in additional increases in FEV₁ as compared with maximum FEV₁ after Turbuhaler treatment (*p*<0.01), indicating that maximum bronchodilation had not been achieved by any of the Turbuhaler treatments.

The results were similar for FMEF, PEFR, and FVC except that the change in FMEF after inhalations at 31 l/minute was significantly lower than the change in FMEF after inhalations at 60 l/minute. Furthermore, the increase in FVC after inhalations at 22 l/minute was similar to that measured after inhalations at 60 and 31 l/minute.

PIFR OF NORMAL CHILDREN

PIFR varied significantly with age (*r*=0.83; *p*<0.01) (fig 2) and with PEFR (*r*=0.90; *p*<0.01). In addition, inhaled volume was found to correlate significantly with FVC (*r*=0.79; *p*<0.01). Fifteen out of 57 children <6 years of age were unable to generate an inspiratory flow rate of 28 l/minute. Apart from

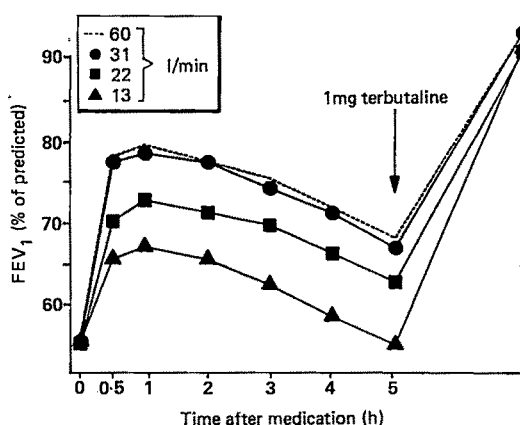


Figure 1 Mean FEV₁ as a percentage of the predicted value after inhalation of 0.25 mg terbutaline from a Turbuhaler at four different flow rates. At five hours 1 mg terbutaline was inhaled from a Nebuhaler.

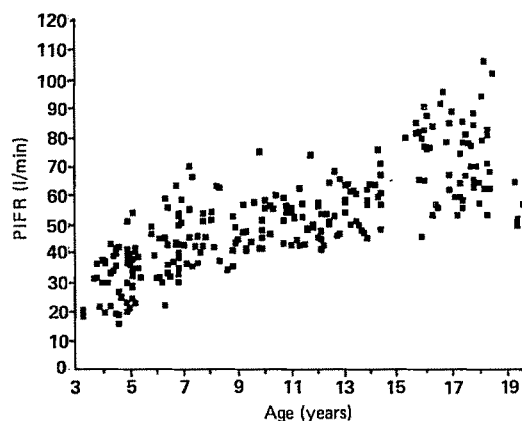


Figure 2 PIFR through a Turbuhaler in various age groups of 265 normal children.

one 6 year old child, who generated an inspiratory flow rate of 22 l/minute, the inspiratory flow rates of the remaining 208 children ≥ 6 years were higher than 31 l/minute.

ACUTE ASTHMA

Mean PIFR measured during the acute attacks of bronchoconstriction in 15 children aged 4 and 5 years (mean PEFr=87 l/minute) was 24 l/minute (range 14–36 l/minute). Nine of these children could not generate an inspiratory flow rate of 28 l/minute. This was also the case for two of 19 wheezing children ≥ 6 years. The remaining 17 children in this age group all generated inspiratory flow rates between 30 and 54 l/minute (mean=39 l/minute). Mean PEFr in the older children was 135 l/minute (range=80–180 l/minute).

Discussion

When the influence of inspiratory flow rate was studied we used half the normal terbutaline dose in the Turbuhaler. On no occasion did this dose result in maximum bronchodilation. Therefore, the comparison between the four treatments took place on the steep part of the dose-response curve where differences are detected more easily than if maximum bronchodilation had been achieved by the Turbuhaler treatment. Under these conditions it was found that the effect of the Turbuhaler was retained down to inspiratory flow rates around 30 l/minute whereas inspiratory flow rates from 30 l/minute and downwards were associated with a decreasing response. This is in good accordance with the results of various in vitro studies showing that although the dose delivered from the Turbuhaler does not vary with flow rate, the amount of respirable drug particles ($<5 \mu$) decreases with decreasing flow rate so that the amount of particles $<5 \mu$ is about 50% lower at flow rates around 22 l/minute as compared with flow rates around 60 l/minute (Astra, personal communication). Therefore, the reduced effect at low inspiratory flow rates seems to be due to insufficient breaking up of the large drug particles in the mouthpiece insert due to insufficient energy supply from the inspiration. We do not know exactly at which flow rate the Turbuhaler will stop working but it still retained about 33% of its effect at flow rates around 13 l/minute, which is well beyond the lowest flow rate measured in any of the 265 normal children and most of the 34 asthmatic children with acute wheeze. For comparison the Rotahaler (Allen and Hanburys) has earlier been found to retain only about 10% of its maximum effect at inspiratory flow rates around 40 l/minute—a flow rate

that about a quarter of children younger than 6 years could not generate.¹

Our findings showed that children should be taught to inhale as fast as possible when using the Turbuhaler. Such advice is simple and, due to the rather high resistance of the inhaler, will not result in unacceptably rapid inspiratory flow rate, which would increase the likelihood of a more central deposition of drug in the bronchial tree.^{3,4}

Virtually all children ≥ 6 years were able to generate an inspiratory flow rate of 30 l/minute, indicating that they would all be able to benefit optimally from Turbuhaler treatment. About a quarter of children aged 3–5 years, however, could not generate this inspiratory flow rate under basic conditions. Further, this number was even higher during attacks of acute bronchoconstriction or in periods of poor control of symptoms. Therefore it will be necessary to increase the inhaled dose or to use other inhalation devices in such situations in the younger age groups. This is in accordance with the recommendations with other powder inhalers,^{1,2} though there seem to be differences between the various inhalers in their susceptibility to a reduced inspiratory flow rate and critical flow rate beyond which the inhaler will not work at all.⁵

A reduction in inhaled volume of 0.5 l has earlier been found not to affect the response from Turbuhaler treatment.⁶ Therefore, it is most unlikely that the small difference in inhaled volume between treatments at inspiratory flow rates around 22 l/minute and treatments at higher flow rates influenced the results in the present study.

We conclude that asthmatic children using a Turbuhaler should be taught to inhale as quickly as possible. Young children may gain less benefit from the treatment because they cannot generate sufficiently high inspiratory flow rates through this inhaler, especially during episodes of acute bronchoconstriction. This may also be the case for a few older children during episodes of severe wheeze.

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High dose pancreatic enzymes in cystic fibrosis

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Abstract

Seven patients with cystic fibrosis taking high doses of pancreatin supplements were assessed to determine whether this dose was necessary to achieve adequate fat absorption. Patients reduced their intake from a group mean of 45 to 21 capsules a day. Five patients did not have any significant alteration in fat malabsorption while taking the reduced enzyme dose.

While 90% of patients with cystic fibrosis require pancreatic enzyme (pancreatin) supplements, wide interpatient variation in the individual dosage requirement exists. Most clinicians rely on symptoms such as failure to gain weight or the passage of offensive bulky bowel actions to regulate the enzyme dose. By increasing enzyme dose in the face of such symptoms the clinician is making two assumptions. Firstly, that the symptoms are due to insufficient pancreatic enzyme function in the small bowel, and secondly that a further increase in enzyme administration will improve fat absorption. However, abdominal symptoms in patients with cystic fibrosis are not invariably related to pancreatic enzyme insufficiency.^{1,2} Increasing enzyme supplementation in the presence of such abdominal symptoms would not be expected to relieve the symptoms or to improve absorption.

The cystic fibrosis clinic at the Royal Children's Hospital, Melbourne, cares for approximately 350 children below the age of 18 years. We were concerned that some of our patients were taking excessive doses of pancreatin supplementation unnecessarily. We therefore studied a group of patients taking high doses of enzymes to determine whether a reduction in the enzyme dose could be achieved without a deterioration in fat absorption. This study was performed as a preliminary to an investigation of patients unable to achieve normal fat absorption despite taking large quantities of pancreatic enzymes.

Patients and methods

Seven patients with cystic fibrosis (mean age 10.7 years, range 9–14 years) who were taking large doses of pancreatin were studied. Patients were included if they had persistent abdominal symptoms, such as offensive bulky stools or abdominal pain, failure to gain weight, or because of concern that they may not require their high enzyme input (table 1). Two patients (cases 5 and 6) presented at birth with meconium ileus, which required limited bowel resection. All patients had a daily fat intake exceeding 2 g/kg and documented fat malabsorption, which improved with the addition

Table 1 Anthropomorphic data

Case No	Age (years)	Sex	Reason for enrolment
1	11	M	Abdominal pain, offensive stools
2	9	M	Failure to gain weight
3	11	M	High enzyme intake
4	14	M	Abdominal pain, offensive stools
5	9	M	Offensive stools, high enzyme intake
6	11	F	Poor weight gain, high enzyme intake
7	10	M	Abdominal pain, high enzyme intake

of enzyme supplements. All were currently taking pancreatin supplements in the form of enteric coated microspheres (Pancrease, Cilag, 5000 units lipase/capsule).

Two outpatient three day faecal fat balance studies were performed, separated by a minimum of three weeks and a maximum of six weeks. Before the second study patients were counselled how to reduce their enzyme dose, following an individual regimen, to approximately 30 capsules per day. The selection of 30 capsules as the modified dosage was arbitrary but is a figure frequently suggested at cystic fibrosis meetings as a maximal dose. The modified enzyme regimen was used for five days before the faecal collection commenced. Faecal fat analysis was performed using the acid titration method of van de Kramer *et al*³ and oral input of fat was determined using the Microdiet programme (Department of Statistics and Mathematics, University of Salford), modified for local food values.

Informed consent was obtained from each patient and at least one parent before enrollment. The study protocol was approved by the hospital ethics committee.

Results

All parents and the older patients enrolled in this study expressed concern at the start of the study as to the likely occurrence of offensive stools and abdominal pain with the reduction of the enzyme input. Patients reduced their intake of pancreatin from a group mean of 45 capsules per day to a group mean of 21 (table 2).

Five patients had normal fat absorption on their usual pancreatin dose while two had considerable malabsorption. Five patients did not have any appreciable alteration in fat malabsorption while taking the modified enzyme schedule. These included four with normal absorption and one with 16% malabsorption on the usual enzyme dosage. The two remaining patients experienced large increases in fat malabsorption with the reduction in enzyme dosage. Fat intake was not appreciably different in the two study periods.

The two patients who had previous bowel resection for meconium ileus both achieved

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Table 2 Number of pancreatin capsules* taken and fat malabsorption (%) while taking usual and modified pancreatin doses

Case No	Usual pancreatin dose		Modified pancreatin dose	
	No of capsules	% Malabsorption†	No of capsules	% Malabsorption†
1	39	5	18	6
2	37	16	18	18
3	51	8	20	39
4	45	22	27	43
5	50	7	28	5
6	44	7	19	10
7	46	5	19	6

*Capsule numbers refer to an average daily intake.

†% Malabsorption refers to the percentage of orally ingested fat malabsorbed, as determined by a three day fat balance study.

reductions in their enzyme intake without appreciable alteration in their absorption. Both these patients achieved normal fat absorption with the reduced enzyme dose.

Discussion

This study has shown that some patients with cystic fibrosis take inappropriately high doses of pancreatic enzymes and that reduction of this high input may be achieved without deterioration in fat absorption. However, two of the patients did have an increase in fat malabsorption when their enzyme dose was decreased. This argues against a policy of setting an arbitrary limit to the enzyme dose, as is frequently suggested at cystic fibrosis clinical meetings. All patients in this study had reached their current dose of enzymes in response to symptoms perceived as due to residual malabsorption. This study highlights the risks of assuming that abdominal symptoms in patients with cystic fibrosis are invariably due to pancreatic enzyme insufficiency and therefore will respond to an increase in enzyme treatment; five of the seven subjects had normal absorption despite persisting symptoms.

The major implication of the results of the present study is that objective assessment of nutrient absorption should be routine in patients with cystic fibrosis, particularly those with abdominal symptoms. The best of the

currently available tests is the three day faecal fat balance. This procedure is time consuming, prone to large errors if not performed correctly, and rarely welcomed by patients. The results of the present study, however, illustrate the importance of assessing changes in enzyme treatment by direct measurements of nutrient absorption.

In conclusion the present study has shown that some children with cystic fibrosis may be taking inappropriately high doses of pancreatic enzymes because of abdominal symptoms not directly related to exocrine pancreatic insufficiency. It is important to determine whether symptoms are due to fat malabsorption and that increases in enzyme replacement result in improved absorption. Recognition of other potential causes of abdominal symptoms in cystic fibrosis should lead to a more logical approach to the patient with residual symptoms on standard enzyme treatment.

The authors wish to thank Mrs B Crawford who performed the faecal fat assays. This work was supported by a grant from the Royal Children's Hospital Research Foundation. The financial assistance of Organon is gratefully acknowledged.

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Dexamethasone treatment for congenital adrenal hyperplasia

M C Young, I A Hughes

Abstract

Ten patients with congenital adrenal hyperplasia (three males, seven females; aged 12-29 years) had their usual glucocorticoid treatment changed to dexamethasone in three crossover dosage regimens. A starting dose of 5 µg/kg/day is suggested but as no one dose regimen resulted in adequate control the timing of the dose must be decided for each patient.

The optimum glucocorticoid preparation, total daily dose, and dose schedule for the treatment of congenital adrenal hyperplasia remain

controversial.¹ Hydrocortisone is probably the preparation of choice in infancy and childhood, but in adolescents near completion of growth and adults dexamethasone may be a convenient alternative.¹⁻³ The potency of dexamethasone in relation to both pituitary-adrenal suppression and side effects is much greater.

Patients

Ten patients (three males and seven females) aged 12-29 years with 21-hydroxylase deficiency (classic salt losing type) congenital adrenal hyperplasia took part in the study.

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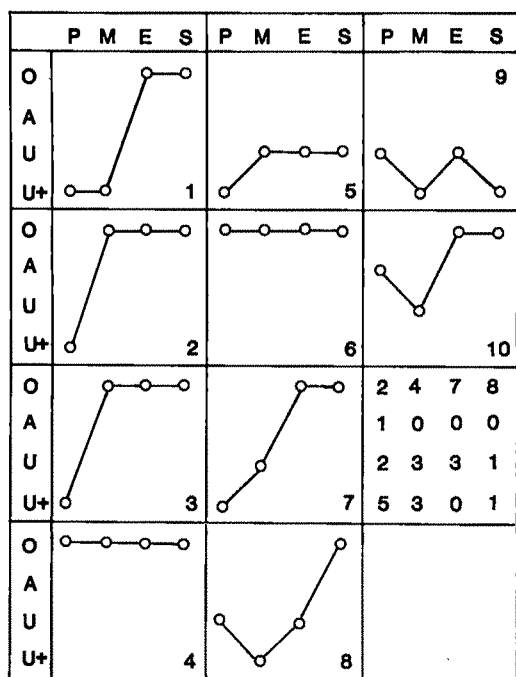
Patients had been previously treated with multiple daily doses of hydrocortisone and were changed to dexamethasone when growth was complete or because there was difficulty in achieving adequate control (this was found mainly in postmenarchal girls in whom menses were irregular). Each patient had an adult bone age.

Profiles of 17OH-progesterone concentrations in blood spot and saliva samples collected at 0800, 1200, 1800, 2200 hours on two consecutive days, and a single measurement of plasma testosterone concentration at 0900 hours (females only), were used to assess the degree of therapeutic control immediately before starting dexamethasone, 10 µg/kg/day. The total amount was given orally at 0900 for one month, at 2100 hours for one month, and in equally divided doses at 0900 and 2100 hours during the third month of the study. The steroid profiles were repeated at the end of each one month period and the results compared with previously published reference values for adequacy of control.⁴

Capsules containing 100 µg of dexamethasone were used to achieve accurate dosage. Patients thereafter reverted to a single morning dose of dexamethasone with the total daily dose adjusted according to the results of regular steroid profiles determined during the ensuing year.

Results

The degree of therapeutic control achieved during each treatment regimen is shown in the



The degree of therapeutic control in 10 patients with congenital adrenal hyperplasia. Control was scored as: O=over-treated; A=adequately treated; U=undertreated; and U+=considerably undertreated. The treatment regimens were: P=previous hydrocortisone treatment; M=morning dose of dexamethasone alone; E=evening dose alone; and S=split dose of dexamethasone (morning and evening). The results in 10 patients are depicted in boxes 1-10; a summary of the entire group is shown in the final box.

figure. Six patients were undertreated while on hydrocortisone. The individual patient scores suggested an increased tendency to overtreatment with dexamethasone, particularly when the dexamethasone dose was given in the evening and as a split daily dose. No one dose regimen appeared to result in adequate treatment.

The long term use of the single morning dexamethasone dose required a reduction in the total daily dose (to <10 µg/kg/day) in five patients and an increase in the dose in one patient before adequate therapeutic control was achieved. All patients reported an increased appetite during this period of stabilisation, and four gained an abnormal amount of weight. An additional patient developed skin striae and mild hirsutism. The final dose requirement of dexamethasone ranged from 0.2-0.75 mg/day; nine patients needed <0.5 mg/day to ensure adequate control.

Discussion

Dexamethasone is a synthetic glucocorticoid whose increased potency and longer half life offer the advantages of superior compliance and regulation of menses in older adolescent and adult women with congenital adrenal hyperplasia. Possible growth inhibiting effects are not relevant at this age. Doses which range between 0.25-0.75 mg/day are usually adequate.¹⁻³ In this study, 10 µg/kg/day of dexamethasone produced a dose range of 0.35-0.8 mg/day. When dexamethasone was started at this dose, given initially in the morning, there was no significant improvement in therapeutic control. There was also a considerable patient idiosyncrasy. More patients appeared to be over-treated, particularly when the dexamethasone was given in the evening (either as a single or split dose). A cumulative effect of the steroid may have been achieved by this stage of the study. The evening administration of glucocorticoid is considered to be more potent because of greater suppression of early morning adrenal steroid concentrations, although dose division and time appear to be unimportant factors when hydrocortisone is used.⁵ Dexamethasone has been successful in achieving adequate control when used either once or twice daily.^{2,3} The need to reduce total daily dose due to cumulative effect, and the minor side effects of dexamethasone have been noted previously.²

A change to dexamethasone treatment when growth is complete often leads to improved ovarian function in women and offers an easier option for compliance in all patients with congenital adrenal hyperplasia. We suggest a starting dose of 5 µg/kg/day and it may be necessary to use especially prepared 100 µg capsules. The dose should be adjusted subsequently in increments not greater than 100 µg according to serial biochemical parameters of therapeutic control.⁴ The choice of dose division and timing remains a matter for each individual patient, but the possible effects of changes in dose timing on therapeutic control must always be considered.

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Sialic acid storage disease

P D Cameron, V Dubowitz, G T N Besley, A H Fensom

Abstract

A baby girl with coarse facial features, hepatosplenomegaly, and developmental delay had raised free sialic acid concentrations in her urine and cultured fibroblasts. She died aged 13 months. Sialic acid is an important constituent of many glycoproteins and glycolipids; impaired release from the lysosome may be the underlying biochemical defect.

Disorders of sialic acid metabolism fall into four categories. Raised concentrations of bound sialic acid are found in conditions associated with neuraminidase deficiency.¹ No enzyme deficiency has been shown in three other categories where raised concentrations of free sialic acid are found: Salla disease, sialuria, and severe infantile sialic acid storage disease. Salla disease, named after an area in northern Finland, comprises progressive psychomotor retardation with lysosomal storage in patients reaching adult life.² Two cases of sialuria have been described where only sialic acid in the urine was raised. These patients had coarse facies, hepatosplenomegaly, a mild clinical course, and no lysosomal storage.³ This case report concerns the fourth category: severe infantile sialic acid storage disease.

Case report

The baby girl was the second child of healthy unrelated white parents; her brother, aged 2 years, was normal. Pregnancy was complicated by premature labour at 32 weeks' gestation; breech presentation necessitated a caesarean section. Birth weight and head circumference were both below the third centile. Resuscitation with intubation was required for five minutes. Initial problems included transient tachypnoea and episodes of cardiac failure with dusky spells and hepatomegaly. Chest radiographs showed cardiomegaly and pulmonary plethora. Transfusion was required for anaemia.

Dysmorphic features comprised hypertelorism, prominent epicanthic folds, strikingly fluffy eyebrows, a long philtrum, and a high arched palate (figure). Facial features were generally coarse. She had short stubby fingers and a square set thumb. Her skin was pale with wispy orange hair.

Diuretics and fluid restriction controlled her



Dysmorphic features showing coarse facies, wispy hair and eyebrows, and telangiectasias.

cardiac failure and she was discharged home at 8 weeks. She was readmitted at 11, 13, and 16 weeks with chest infections and cardiac failure. Hepatosplenomegaly and telangiectasias had become prominent. She developed a need for supplemental oxygen, and weight gain remained poor. By 5 months she had rarely smiled, she remained hypotonic, visual following was poor, and auditory response was absent.

Laboratory investigations at 5 months included measurement of blood concentrations of urea, electrolytes, and haemoglobin, liver function, blood and urine amino acids, urine mucopolysaccharides, and lactate. Chromosome analysis, iron studies, thyroid function tests, and lysosomal enzyme activities were also performed. All studies gave normal results. Skeletal survey, cranial ultrasound, and nitrogen washout tests were also normal. Chest radiography showed fine hazy shadowing in the lung fields and cardiomegaly. Ophthalmic examination showed an intermittent divergent strabismus.

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Sialic acid concentrations in urine and cultured fibroblasts

	Patient	Controls	
		Mean	Range
Urine ($\mu\text{mol}/\text{mmol}$ creatinine)			
Free	994	93, 78	
Bound	109	71, 52	
Fibroblasts (nmol/mg protein)			
Free	25	2.6	1.5–6.7 (n=9)
Bound	17	8.6	6.5–10.7 (n=5)

Sialic acid concentrations were measured by the thiobarbituric acid method⁴ before and after hydrolysis.

mus and a pale retina. Blood smears showed vacuolated lymphocytes, monocytes, and neutrophils. A bone marrow specimen also showed vacuolated cells and an excess of eosinophils. The free sialic acid concentration of cultured fibroblasts and urine was raised (table), and a diagnosis of severe infantile sialic acid storage disease was made.

Subsequent clinical progress was poor. She remained extremely hypotonic and was socially unresponsive. Oxygen requirement persisted, and she eventually died with bronchopneumonia at 13 months. Permission for necropsy was refused.

Discussion

Stevenson *et al* described two unrelated cases of severe infantile sialic acid storage disease and reviewed five other cases in 1983.⁴ The main features he identified were coarse facies, growth delay, appreciable mental retardation, hepatosplenomegaly, recurrent pneumonias, and in five, evidence of lysosomal storage with raised

free sialic acid in cells and urine. The infant reported here displayed all these features, and she also showed a more pronounced respiratory impairment. Cardiac failure was also prominent, suggesting either a storage disorder of the myocardium, or a response to the respiratory problems. The presence of multiple widespread telangiectasias, presumably related to liver disease, is also a new finding.

The exact role of sialic acid in cellular function is unclear, but it is known to be an important constituent of many glycolipids and glycoproteins. It has been suggested that the underlying defect is impaired transport of free sialic acid across the lysosomal membranes, but the precise defect has yet to be identified.⁵ Antenatal diagnosis is available by assaying free sialic acid in amniotic fluid or by chorionic villus biopsy.⁶ Severe infantile sialic acid storage disease should be considered in a child presenting with coarse facial features, growth and developmental delay, hepatosplenomegaly, and evidence of abnormal storage in cells.

We are grateful to Dr AW Boon for allowing us to report his patient.

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Acute liver failure induced by carbamazepine

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Abstract

Two children developed acute liver failure while taking carbamazepine. Clinical and laboratory findings suggested an immunological reaction, but only one child improved on steroids. Determination of liver function during the first few weeks of treatment and early detection of signs of idiosyncrasy may prevent this rare but severe complication.

Since 1970, 14.5 million adults and children are estimated to have taken carbamazepine. Unwanted effects mainly or exclusively affecting the liver have been reported in 499 instances, but often other causes of liver damage were not excluded. In about half of these cases alteration in the results of liver function tests was the only abnormality reported (Ciba-Geigy, personal communication). There have been 17 deaths from liver disease, five in children,^{1 2}

but in only one of these was carbamazepine the sole hepatotoxin. We describe two children receiving carbamazepine who developed life threatening liver disease.

Case reports

CASE 1

A girl aged 11.6 years developed a severe maculopapular rash, intermittent fever, arthralgia, cough, anaemia, anorexia, diarrhoea, and vomiting four weeks after starting carbamazepine (16 mg/kg/24 hours) for focal epilepsy. Her medical history was negative. Carbamazepine was stopped, the blood concentration being 32 $\mu\text{mol}/\text{l}$ (therapeutic range: 16–50 $\mu\text{mol}/\text{l}$). Two weeks later she developed jaundice. On admission, six days later, she was pale and jaundiced, with a generalised exfoliative rash, periorbital oedema, generalised lymphadenopathy, and stomatitis. Firm liver and spleen

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edges were palpable 6 and 7 cm below the costal margin. Temperature was 38.5°C. Her haemoglobin concentration was 76 g/l; red cell indices, reticulocyte, white cell, platelet, and differential counts were normal, with no eosinophilia; prothrombin time was 20 seconds (control 13 seconds).

Biochemical investigations were as follows (reference range in parentheses). Total bilirubin concentration was 212 $\mu\text{mol/l}$ (<20) with a conjugated fraction of 198. Activities of enzymes were: aspartate aminotransferase 165 IU/l (<50); γ glutamyl transpeptidase 299 IU/l (<50); and alkaline phosphatase 407 IU/l (<300). Albumin concentration was 31 g/l (35–50) and concentrations of plasma sodium and proteins were normal. Concentration of IgA was normal but IgG, IgM, and IgE were increased (22.3 g/l, 5 g/l, and 30 kU/l (<18, <2.2, and <10) respectively). C3 and C4 complement components were decreased (0.35 g/l and 0.13 g/l (0.55–1.2 and 0.20–0.60) respectively). Autoantibodies were negative. A $^{99\text{m}}\text{Tc}$ colloid liver scan showed reduced liver uptake, with increased bone and spleen uptake. Bone

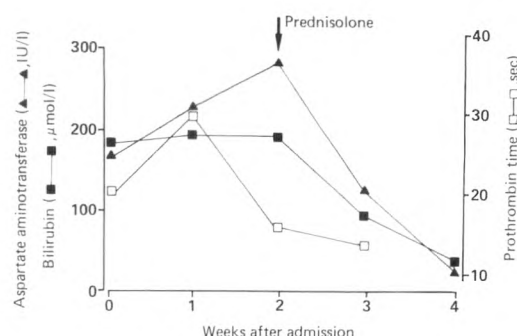


Figure 2 Effect of prednisolone treatment on serum aminotransferase, bilirubin, and prothrombin time in case 1.

marrow aspirate contained many plasmacytoid lymphocytes and moderate erythrophagocytosis by macrophages. A specimen taken at liver biopsy, performed 12 days after admission, showed an acute hepatitis, with both portal and parenchymal cell infiltrates rich in plasma cells (fig 1A). After 10 days of supportive treatment (blood and albumin transfusions, oral iron, Ketovite (Paines and Byrne), and intravenous vitamin K) without improvement, she was given prednisolone (0.7 mg/kg/24 hours). This was followed by a dramatic symptomatic and biochemical improvement, although the prothrombin time had already returned to normal before starting steroid treatment (fig 2). She was discharged one week later after complete resolution of symptoms. Her serum bilirubin concentration was 31 $\mu\text{mol/l}$, γ glutamyl transpeptidase 214 IU/l, and aspartate aminotransferase, alkaline phosphatase, albumin, and prothrombin time were normal. Prednisolone was stopped after 18 days. Three years later the girl is well with normal liver function.

CASE 2

A girl aged 7.8 years presented with fever, generalised maculopapular rash, arthralgia, and lymphadenopathy four weeks after starting carbamazepine (16.5 mg/kg/24 hours). Seventeen days later she developed jaundice, ascites, and generalised oedema. She had had convulsions from the age of 8 months. At 3 years grand mal epilepsy was diagnosed. She received sodium valproate for two months at the age of 7 years, but she had been on no anticonvulsant treatment for four months before starting carbamazepine. On admission she was jaundiced, with generalised peeling maculopapular rash, oedema, and ascites. A firm liver was palpable 3 cm below the costal margin; her spleen was not palpable.

Concentrations of carbamazepine in the blood was 28 $\mu\text{mol/l}$. Her haemoglobin concentration was 105 g/l with normal white cell, platelet, and differential counts; there was no eosinophilia, and the prothrombin time was 24 seconds (control 15 seconds). Total bilirubin concentration was 236 $\mu\text{mol/l}$ and activities of aspartate aminotransferase 946 IU/l, γ glutamyl transpeptidase 206 IU/l, and alkaline phosphatase 151 IU/l. Ammonia was 94 $\mu\text{mol/l}$ (10–47), total protein 43 g/l, albumin 24 g/l, and plasma sodium 126 $\mu\text{mol/l}$. IgG was 5.9 g/l (6.5–18),

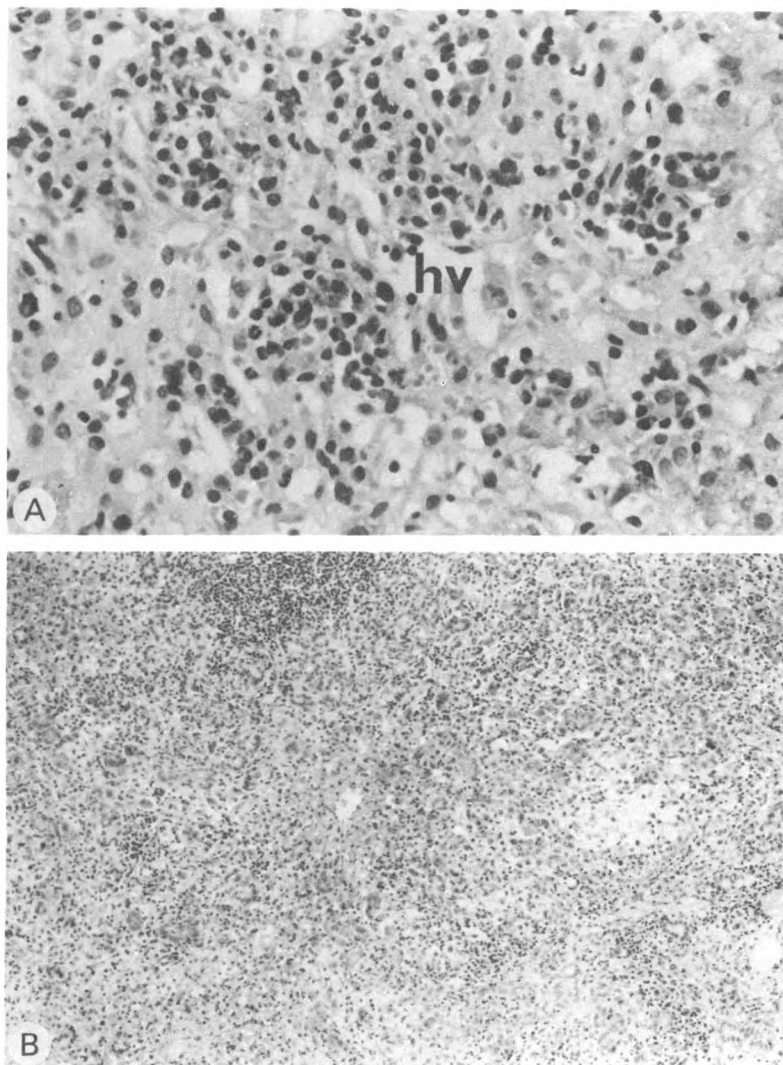


Figure 1 Liver histology. A: section from case 1 showing prominent perivenular cell loss and plasma cell infiltration (hv, hepatic venule). B: section from case 2 showing submassive parenchymal loss with widespread inflammation, scattered bile duct like structures, and only occasional islands of surviving, pale staining hepatocytes. Haematoxylin and eosin stain: A $\times 180$, B $\times 45$.

IgA and IgM were normal, and IgE was raised at 550 kU/l. Autoantibodies were negative. C3 and C4 were 1.5 and 0.19 g/l. She was treated with fluid restriction, vitamin K, cimetidine, albumin and, three days after admission, prednisolone 1 mg/kg/24 hours. Four days after admission grade III hepatic encephalopathy developed and prothrombin time lengthened to 70 seconds. Because of further deterioration, orthotopic liver transplantation was performed 24 hours later when prothrombin time was 120 seconds. The excised liver was shrunken with evidence of submassive necrosis. On histology there was widespread inflammation comprised of lymphocytes, pigmented macrophages, neutrophils, and fewer plasma cells (fig 1B). The child died of infectious complications three months after transplant.

In both cases hepatitis A and B, cytomegalovirus, Epstein-Barr, measles, and leptospira infections were excluded; α_1 antitrypsin phenotype and caeruloplasmin, plasma and urine copper, serum potassium, calcium, phosphate, glucose, cholesterol, creatinine, and urea concentrations, and urinalysis were normal.

Discussion

The diagnosis of liver injury induced by drugs rests on the exclusion of other aetiological factors. In the two children described no other cause of liver damage or drug exposure could be identified.

Hepatic side effects of carbamazepine are very rare. Among them, changes in results of liver function tests, jaundice, and granulomatous or cholestatic hepatitis are the most common.³ In a study of children, a clinically insignificant rise in results of liver function tests was found in 6% of 220 patients.⁴ We have identified only three reported cases of fatal acute liver failure directly attributable to carbamazepine, one being a child.¹ Recently four children with fatal fulminant hepatitis while on carbamazepine were reported.² All were taking several drugs, with three receiving other potentially hepatotoxic drugs, such as phenytoin and pri-

midone. The mechanism of liver injury in carbamazepine hepatitis remains poorly understood, although it is presumed to be an idiosyncratic hypersensitivity,⁵ possibly deriving from genetically determined inability to inactivate toxic metabolites.⁶ Consistent with reports from other authors, we found that clinical presentation and laboratory tests in our two patients suggest an immunoallergic mechanism. Thus both had onset of symptoms four weeks after starting treatment, fever, rash, arthralgia, and raised IgE with carbamazepine concentrations within the therapeutic range. In addition, case 1 had a heavy plasma cell infiltrate found on histology, decreased complement concentration with increased IgG and IgM, and her recovery has been aided by the administration of steroids. In case 2 these features were absent and no response to steroid was observed, possibly suggesting another mode of hepatocyte injury.

Liver function tests performed routinely in the first weeks of carbamazepine treatment, and in the presence of other idiosyncratic reactions to the drug, may help to detect patients at risk of developing this rare complication.

We thank Dr TK Hanid and Dr DM Cook for referring the patients. NH is a British Council Research Fellow, GMV is supported by the M McGough Foundation Against Liver Disease in Children.

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Addendum

Since this paper was accepted we have admitted and successfully transplanted a 3 year old child who had fulminant hepatic failure due to carbamazepine toxicity.

Contractural arachnodactyly with mitral regurgitation and iridodonesis

I C Huggon, J P Burke, J F Talbot

Abstract

An infant girl with arachnodactyly, spontaneously resolving contractures, dolichostenomelia, iridodonesis, and mitral and tricuspid incompetence died in cardiac failure. We confirm that congenital contractural arachnodactyly may exhibit serious cardiovascular and ophthalmic complications like Marfan's syndrome. The presence of iridodonesis further obscures the differentiation between classical Marfan's syndrome and congenital contractural arachnodactyly.

Beals and Hecht described an autosomal dominant syndrome of congenital contractural arachnodactyly distinct from classical Marfan's syndrome.¹ It is characterised by multiple contractures at birth that resolve spontaneously (in 94%), dolichostenomelia, arachnodactyly (in 85%), abnormalities of the external ears (in 65%),² and the absence of the eye and cardiovascular abnormalities typical of Marfan's syndrome. Since then, however, serious eye and cardiac abnormalities that lessen the distinction from Marfan's syndrome have been described.³⁻⁵

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We report a case of congenital contractural arachnodactyly complicated by iridodonesis (shimmering iris) and anterior megalophthalmos (enlarged anterior segment).

Case report

An infant girl was delivered normally at term after an uneventful pregnancy with normal liquor volume. She was the fourth child of healthy 25 year old unrelated parents and the other siblings (age 8, 5, and 4 years) were normal. Her birth weight was 3750 g (>50th and <75th percentile) and length was 57 cm (3 cm >97th percentile). She had gross arachnodactyly (fig 1), dolichostenomelia, prominent symmetrical flexion contractures of the knees, hips, elbows, and ankles, and appreciable enophthalmos. The ears were unremarkable. A loud pansystolic murmur and click were present and cardiac ultrasound demonstrated mitral and tricuspid regurgitation; skeletal survey showed arachnodactyly. Chromosome studies and urinary homocystine concentrations were normal.

From the age of 6 weeks she required diuretic treatment for cardiac failure. There was failure to thrive, but her developmental milestones were not significantly delayed. She was noted to have iridodonesis. Ophthalmic examination at this time and at 4 months confirmed iridodonesis in association with anterior megalophthalmos, alternating divergent squint (fig 2), myopic astigmatism, normal fundoscopy, and no evidence of lens subluxation on slit lamp biomicroscopy. She fixed and followed objects with each eye.

There was a gradual spontaneous improvement in all her joint contractures with time. Hospital admissions with persisting vomiting or

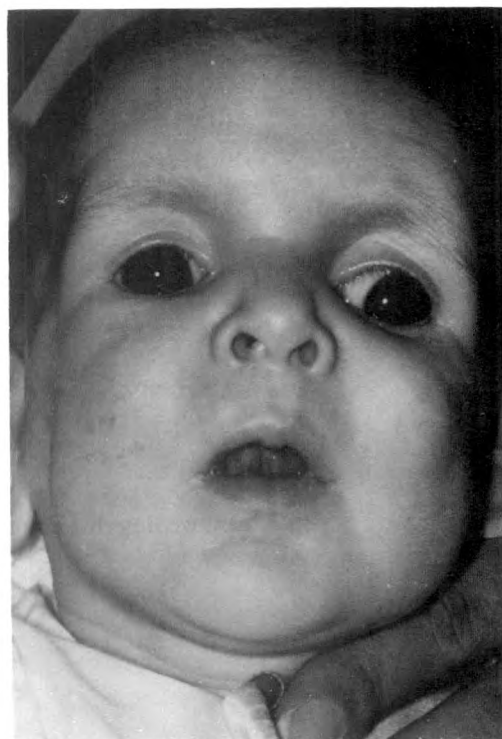


Figure 2 Infant with enophthalmos, alternating divergent squint, and megalocornea at 3 months of age.

exacerbations of cardiac failure were frequent and she died aged 4 months.

Permission for necropsy was limited to examination of the heart. This confirmed incompetence of the mitral and tricuspid valves. The chordae tendineae attached to the posterior leaflet of the mitral value had ruptured permitting prolapse into the left atrium, which was thought to be the immediate cause of death.

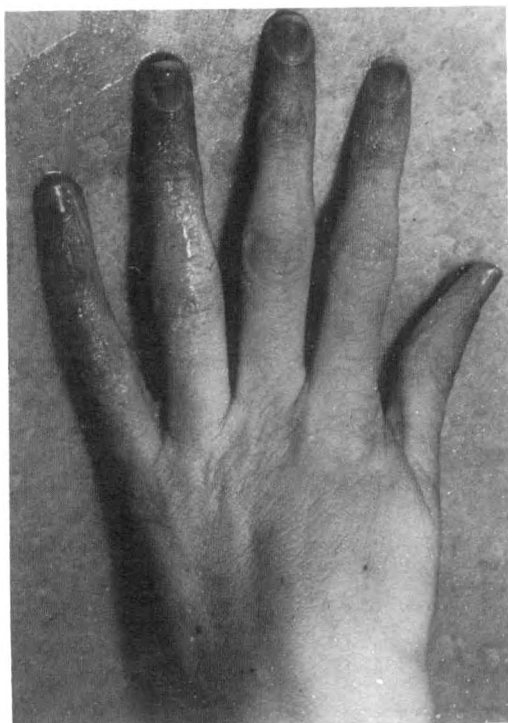


Figure 1 Hand showing gross arachnodactyly.

Discussion

The condition of this 4 month old infant with resolving congenital contractures, arachnodactyly, fatal mitral regurgitation, and iridodonesis presumably arose as a spontaneous mutation. In the original description of congenital contractural arachnodactyly the authors argued that the absence of severe cardiac and ophthalmic abnormalities helped to distinguish congenital contractural arachnodactyly from Marfan's syndrome and indicated a better prognosis in the former.¹ Subsequent reports of congenital contractural arachnodactyly in patients with mitral valve prolapse⁵ and regurgitation,⁴ keratoconus,³ and myopia⁵ have blurred this distinction. The presence of congenital symmetrical contractures at birth maximally involving the knees and enophthalmos, as in our case, favours the diagnosis of congenital contractural arachnodactyly.

The concept that congenital contractural arachnodactyly and Marfan's syndrome are separate entities is challenged by the kindred described by Bass *et al*, where one family member appeared to satisfy better the criteria for Marfan's syndrome while the remainder had congenital contractural arachnodactyly.³ Until specific biochemical or genetic abnormalities,

or both, are identified that differentiate these syndromes their separate existence based on clinical criteria alone will be disputed by some.

Before this report, iridodonesis, which is usually associated with lens subluxation, has only been described in cases with Marfan's syndrome. The iridodonesis in our patient appeared secondary to anterior megalophthalmos, rather than to isolated lens subluxation. Anterior megalophthalmos has occurred rarely in Marfan's syndrome,⁶ but has not been previously described in congenital contractural arachnodactyly. Slit lamp biomicroscopy is helpful in distinguishing these abnormalities.

Although patients with congenital contractural arachnodactyly are less likely than those with Marfan's syndrome to develop serious ocular and cardiovascular complications, the case we describe emphasises the importance of serial cardiovascular and ophthalmic assessment

of all these patients and further blurs their clinical separation.

We wish to thank Dr B A M Smith for permitting us to write this report on his patient.

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PERSONAL PRACTICE

Checking the health of school entrants

K Whitmore, M C O Bax

For almost 70 years until 1974 children were legally obliged to be examined by a doctor at school. Among the reasons for this were 'the early detection of unsuspected defects' and 'checking incipient maladies at their outset'.¹ At one time statutory regulations required routine periodic medical inspections at three specified ages between entering and leaving school, but from 1959 local education authorities were allowed to introduce more selective arrangements. These became the vogue in the 1960s for children during their middle school years but only one education authority opted for selective rather than routine medical examinations of children on entry to school. Until five years ago 90% of district health authorities still favoured routine examinations at this stage (C R Haines, personal communication). Furthermore, as a result of the greatly improved physical health of schoolchildren and the relative increase in developmental and behavioural disorders, school doctors have been paying more attention at these entrant examinations to the children's cognitive and social development; such developmental assessment has long been an important feature in the programme of health care for preschool children.

There is now mounting evidence, both factual and hearsay, for either the adoption of selective medical examinations of school entrants or even the elimination of examination by a doctor and reliance on a routine health check by school nurses. For instance, O'Callaghan and Colver in arguing for selective medical examinations maintain that at the age of 5, new important treatable abnormal physical conditions that can only be detected by a doctor are too rare to justify a doctor seeing all school entrants.² They also maintain that the more common disorders of learning and behaviour are too difficult for a doctor to assess at their examinations, and that such assessments are anyway unnecessary as the disorders invariably come to light in the course of time in school, and their assessment is strictly the responsibility of educational psychologists.

The British Paediatric Association (BPA) also considers routine entrant medical examination unnecessary if an effective preschool service has been established and medical information is efficiently transmitted between preschool and school health services.³ The BPA did not suggest that this is generally the case at present but even before their advice had been given a number of health authorities had abandoned these examinations. This step had been precipi-

tated by a serious shortage of funds but rationalised by popular misconceptions about screening and the role of the doctor in promoting health. Their argument goes something like this: the doctor's examination is no more than a screening procedure; screening is a paramedical function best carried out by nurses because a school nursing service is probably more cost effective than the employment of doctors to carry out regular school medicals; this saves the authority money but it also leaves the doctors more time for more important aspects of educational medicine, which suits them because they see the work in terms of diagnosis and treatment of disease.²⁻⁷

This argument is specious—and not only because it results in a reduction rather than a redeployment of medical time; in this and in other ways it can only lead to a further deterioration in the quality of care from a service already severely compromised as we shall hope to show in answering the following three questions:

- (1) How effective might nurses be in identifying problems?
- (2) Does it matter if neurodevelopmental problems are missed?
- (3) How much money might be saved by nurse only health check of entrants?

(1) How effective might nurses be in identifying problems?

It is not of course true that a doctor's examination of all school entrants is no more than a screening procedure, as generally understood and meeting agreed criteria.^{8,9} It is a clinical procedure requiring a considered judgment (assessment) of each child's state of health, and therefore better referred to as a health check.¹⁰ Checking entrants' health is not the sole prerogative of doctors but when carried out by nurses it still does not become just a population screening however often this is incorrectly said to be so. Both doctors and nurses may occasionally use genuine screening techniques in checking health.

Nevertheless, absence of disease remains one characteristic of health and so the early identification of unsuspected or incipient disorder (developmental and behavioural no less than physical and sensory) has to be one objective of a health check. If it is to be left entirely to the nurses we have to be sure that they can identify any disorder (that is, recognise or suspect its

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presence) as certainly as doctors. One previous American study in particular showed how mass screening (so called) by health aides identified a greater number of problems than did physical examinations (by trained school nurse practitioners),¹¹ but the examinations identified more problems per 100 contacts and 85% of those problems were of a kind for which screening was inappropriate. These findings were from a study of schoolchildren of all ages, not solely entrants, and did not include neurodevelopmental testing.

In the absence of data from other prospective studies we have looked back at our own data from a study of health service needs in 12 primary schools in Paddington, an inner city district of London, in which 351 school entrants were examined by doctor and nurse.¹² In retrospect we wanted to compare the actual results from these joint examinations with those that theoretically we might have expected had the nurses been responsible on their own for checking health and development. The answer would depend on how much of the examination they could have done alone. We have already described our joint examination in detail,¹³ and obviously they could do all they did then. They perused all available preschool health records; they weighed and measured each child, recording the readings on Tanner-Whitehouse age percentile charts; they tested and recorded near, distant, and colour vision; and they gave each child a pure tone audiometric sweep test (the only true screening technique they employed). They also completed a parent interview schedule (PIS). In retrospect they could certainly have checked each child's weight on Chinn-Morris height percentile charts,¹⁴ and measured head circumference, both of which the doctors did in the study. We could assume also (couldn't we?) that with the child stripped for weighing they could have inspected exposed parts for skin disease and for state of trunk and limbs. We see no reason why they should not have used an auroscope to look for wax or other obstruction in the external auditory meatus; school nurses already do in some districts. Absence of, or uncertainty on perusal of preschool records would have meant automatic referral of the child to the doctor who would have then routinely carried out a comprehensive examination; so would a history of not speaking clearly in sentences by the age of 3 and parental worry about the child's behaviour at home or bedwetting, when the doctor would routinely have done a neurodevelopmental examination. We do not think the school nurse could do such an examination in full, at least not without a lot more training, and it is undesirable that it be carried out piecemeal. For instance, while she could be trained to test speech discrimination it is preferable not to separate this from tests of speech, language, and other aspects of mental development.

The results of nurses' health checks of entrants that might have been expected under the above circumstances are shown in table 1, where they are compared with the actual results from the joint examinations. The latter brought to light 462 problems (suspected disorders) for

Table 1 Nature and number of problems actually identified by joint examinations and theoretically identifiable by nurses' health checks (351 school entrants)

Nature of problem	Identified by joint examination	Identifiable by nurse only health check
Physical conditions	57	45
Failed vision test	37	37
Failed hearing test	58	58
Parent worried about behaviour	39	39
Parent worried about bedwetting	14	14
Total	205	193
Failed speech test	11	9
Failed speech and language tests	34(×2)	20(×2)
Failed language test only	87	36
Delay in cognitive development	91	52
Total No of problems	462	330
No of children with problems	232	182

which 232 children (66% of all the entrants) were given appointments for a review within three months or so. On their own the nurses might have been able to identify 72% of the problems, or more importantly bring before the doctor 78% of the children with suspected disorders.

They could have identified four out of five of the physical conditions, all the sensory, behavioural (including bedwetting) problems and approximately half those relating to delay in speech, language, or cognitive development in so far as these would have been detected if the doctor carried out a neurodevelopmental examination on children referred for the four reasons stated above. Twelve of the physical problems listed separately in table 2 (all but two of which had not been 'suspected' by the parents), would have been missed: five undescended testes, three congenital heart defects, and four ear, nose, and throat conditions. From the PIS and their own observations the nurses might have picked up some of the ear, nose, and throat disorders but not the others; however, at the most this would have increased the proportion of problems identified by only 1% as the great majority of the problems they would have missed were developmental.

(2) Does it matter if developmental problems are missed?

Behind this question lie the issues of whether one can effectively, and if so whether one

Table 2 Physical conditions (n=57) for which 54 children required re-examination

	No of conditions
Growth and nutrition (n=27):	
Overweight	15
Underweight	1
Small stature	11
Medical (n=26):	
Congenital heart disease	4
Celiac disease	2
Asthma	2
Skin disease	5
Genitourinary disease	1
Ear, nose, and throat conditions	6
Undescended testicle	5
Debilitation	1
Orthopaedic (n=4):	
Valgus ankle	2
Deformed finger	1
Posture	1

should, check the development of children when they start school. As health in children has always to be viewed in a developmental context it is inconceivable to us that there should be any doubt about the need to check development when checking physical state; yet the working party on child health surveillance are curiously ambivalent about this.⁵ They argue that developmental screening tests are scientifically unacceptable as they do not meet the required criteria for such tests (especially as regards sensitivity and specificity); and the same applies to unsolicited developmental examinations as these are screening procedures when offered to all children. They then concede that developmental examination *can* effectively identify developmental disorder but dismiss its use as unnecessary and/or irrelevant, and finally recommend only that *repeated* developmental examinations on a routine basis should be discontinued (our italics). More specific objections to developmental examinations are that they are unstandardised, unreliable, and rely on soft neurological signs (for example, clumsiness) for which the range of normality has not yet been clearly defined.^{2 5}

Most of these criticisms stem from the bland but fallacious assumption that any procedure that seeks to identify a disorder (or even a problem, according to the above working party) in a child of which his parents are unaware is a screening procedure and therefore subject to evaluation in terms of the agreed criteria for screening tests^{8 9}—irrespective of the nature or complexity of the procedure and irrespective also of whether or not any such disorder (or problem) meets additional criteria that warrant a screening programme in the first place. This assumption is evident throughout that working party's report but nowhere more blatantly than in their misquote that the working party on school health services also concluded that developmental *examination* on entry to school was unjustified: what the latter actually recommended was that neurodevelopmental *screening* should not at present be used routinely.³

It is true that some of the tests used in developmental examinations are not as well standardised as others, nor perhaps as reliable, but neither are many of the clinical tests used in standard medical practice. Even in this age of technology clinical medicine remains a very inexact science. It would be plainly ridiculous to require all clinical tests used to elicit abnormal signs to have all the characteristics of screening tests. Ways and means of evaluating developmental examinations are certainly still needed and proving elusive but to discredit them as screening procedures is scientifically dishonest. It is a strange idea, too, that these examinations are said to depend upon soft neurological signs, and one far removed from the neurodevelopmental examination we have described in this journal and that Drillien and Drummond employed.¹⁵ In these, responses to tests involving sensorimotor skills and speech and language were observed as well as the child's adaptive and social behaviour; such observations, alongside a developmental history and physical, personality, and experiential factors, were then used in

arriving at a clinical assessment of the child's developmental status. It calls for a package approach rather than the isolated use of single tests, and herein lies a fundamental difference between screening and examining. The clinician, unlike the screener, does not have to rely upon a single abnormal response to conclude an abnormality is present, nor even possibly present and needing referral. The clinical significance of equivocal responses to individual tests that so nullify their use in screening can usually be gauged in the context of responses to other tests, that is, through the exercise of professional judgment on the part of the examiner.

This was well shown from reliability studies that we carried out. High correlations were achieved between the examiners when all items were included in the assessment, but somewhat lower correlations were found when only *abnormal* responses were compared. Thus the finger-nose test proved to be the one where agreement on abnormal responses only reached about 50%. On the other hand validity studies showed that the test contributed significantly to the child failing the whole battery of tests. Judgments about the finger-nose test are difficult but the test along with others helps to identify the clumsy child. These findings are very similar to those reported in studies of more severely disabled children in the neuropsychiatric studies in childhood¹⁶; the examiners had disagreed about individual signs but in general reached the same diagnosis.

Developmental examinations of school entrants have also been condemned because they cannot predict which children will eventually require extra help and because the treatment of neurodevelopmental abnormalities that may be found has no impact on associated language or learning difficulties and anyway the minor abnormalities improve spontaneously.^{2 5} We know opinions differ as to what exactly is the association between neurodevelopmental delay and learning problems but there is convincing evidence that their association is at least statistically very significant.^{15 17 19} From our own observations and research findings we have no doubt that the presence of neurodevelopmental delay is a clear indication of the child's vulnerability to adverse experiences and a predisposition to academic and behaviour problems that may persist into teen ages.²⁰ We are also concerned at its relatively high prevalence, 7%. Clinicians may be reassured by the knowledge that statistically it is very likely that the child's neurodevelopmental delay will have been overcome and that not all children at risk do actually experience educational and social failure. These are not, however, sufficient excuses for defeatist and ostrich like clinical practice and they are no consolation for the substantial number of children who do fail.

Of course their difficulties will eventually come to light in school, though on the whole teachers tend to be reluctant to refer any but the most severely handicapped children for investigation until they have been in junior school for a year or two and are obviously failing and they don't know what else to do. But why should a child have to run this gauntlet when his

difficulties can so often be recognised 'in embryo' by a doctor at an entrant examination? And what about their secondary effect while the maturity of the child's central nervous system is catching up? Have we already forsaken the preventive tradition of health services in school? Making a diagnosis of neurodevelopmental delay does not mean the child has to be labelled with an untreatable disorder nor that eventually he will need special education. Doctors should always be circumspect in what and how they tell parents and teachers; the use of descriptive terms commonly suffices and can form a basis for symptomatic treatment, a pattern of care so frequently resorted to in the case of physical disease. Thus physiotherapy or pharmacology and remedial teaching may help some children in the short term; guidance and support for parents may help to contain family stress and diminish the scapegoating and rejection of the child that so often stem from ignorance and despair. Maybe teachers are still uncertain of what special educational techniques to employ but they will never discover these if they are never faced with the problem; in the meantime giving them a better understanding of the influences governing a child's performance and behaviour in school may help them to adopt a more appropriate stance toward the child. We are frankly amazed that medical colleagues on the working party on child health surveillance should subscribe to the view that this is an inappropriate ineffective task for doctors because they can only perceive developmental delays and impairments as a form of pathology that requires treatment.⁵ Coupled with the findings from a recent survey of general practitioners interest and training in child health surveillance,²¹ it is a disturbing indication of the prejudice that still exists within conventional medicine against the concept of the integration of preventive and curative care in the child health services.

(3) How much money might be saved by a nurse only health check of entrants?

It is possible to estimate and so compare the costs of joint (doctor and nurse) health checks of all entrants to a typical infant school and of health checks by the nurse alone, by extrapolating from data obtained during our study of

health services in Paddington primary schools.¹² A typical health district of 240 000 total population has 100 primary schools within its boundary with 225 pupils per school and an annual intake of 37 children 'rising 5'.

Our joint examination of an entrant takes on average 20 minutes of doctor time and 37 minutes of nurse time. It is seldom feasible for the nurse to test vision (distant, near, and colour, taking five minutes) and hearing (a pure tone audiometric audiometric sweep test taking 10 minutes on average, allowing for a full audiogram on the occasional child who fails the sweep test) when the child and his mother attend a joint examination. In practice it is most convenient for the nurse to do these on a previous day but this does mean that she has also to peruse preschool health records then (taking two minutes). When the parent attends the nurse can then weigh the child, and measure his height and head circumference (taking four minutes), and she has ample time to interview the parent (taking on average eight minutes). As the continuing health care of the child in school will rest principally with the nurse there is much to be said for her being present during the closing stages of the medical examination and discussion with the parent.

Applying (for this theoretical exercise) the *current* hourly rates of pay, based on the full time midpoint salary scales for school nurse and community medical officer (school doctor) excluding London weighting, the cost of such joint health checks of 37 entrants would be £298.81 (table 3).

If the nurse carried out the health check on her own the nursing time required would be much the same (37 minutes) as in a joint check. For in addition to her tasks itemised above (taking 29 minutes) she would need to do a physical inspection (of skin, limbs, and of ears with an auriscope, taking two or three minutes) and she would also need to conclude the check with her own brief discussion with the parent. Even so, this would not mean the authority would save the full cost of the doctor's routine examination of all 37 entrants (that is, £115.19) because there would still be some children needing a medical examination solely as a result of the change to a nurse only check. The cost of these examinations would need to be deducted to arrive at a net saving from nurse only checks.

Table 3 Comparative staffing costs for joint doctor and nurse and nurse only health checks of school entrants in a typical health district

(A) For joint health check at each primary school			
Cost of nurse:	37 children at 37 minutes per child and £7.96 per hour		£181.62
Cost of doctor:	37 children at 20 minutes per child and £9.34 per hour		£115.19
			<u>£296.81</u>
(B) For nurse only health check at each primary school			
Cost of nurse:	37 children at 37 minutes per child and £7.96 per hour		£181.62
Cost of doctor:	(a) Eight children (with no preschool records) at 20 minutes per child and £9.34 per hour		£24.90
	(b) 12 children (with possible problems) at 10 minutes per child and £9.34 per hour		£18.68
	(c) Six children (among those at (b) above) needing neurodevelopmental assessment at 12 minutes per child and £9.34 per hour		£11.20
	(d) 17 children needing check for undescended testicles and/or congenital heart disease, at one boy and one girl per five minutes and £9.34 per hour		£6.63
			<u>£243.03</u>
(C) Difference between costs of joint and nurse only health checks at each primary school			
			<u>£55.78</u>

These extra examinations would be: (a) a 20 minute comprehensive examination of children with no preschool health records (21% of entrants); (b) an investigation of the children referred by the nurse for a specific reason (32.5% of entrants); (c) a 12 minute neuro-developmental assessment of those children referred because they were not speaking clearly in sentences by the age of 3 and/or their behaviour or bedwetting was causing concern to the parents (17% of entrants); and (d) a routine check for undescended testicles and/or congenital heart disease in the remaining 46.5% of entrants, at the rate of a boy and a girl every five minutes (this check can be done on the children in (a) and (b) above at their special examination).

With regard to the children in (b), this initial investigation of a possible problem would have been incorporated into the 20 minute comprehensive examination of each entrant if there had been joint rather than nurse only health checks. The proportion of such entrants used in our calculations allows for the fact that some have more than one possible problem; costs are apportioned to the number of children examined and not the number of problems. The time required by the doctor to examine each child would depend upon the nature of the suspected problems and how many were present. It would be least for children who fail only their vision test and most for those with a speech and/or language problem and worrying behaviour. We have reckoned it would be 10 minutes per child on average. We know that some districts have arrangements whereby some specialists (for example, speech therapists, ophthalmologists) accept referrals direct from school nurses. We think this is medically unsound and a misuse of specialist resources. It happens most often in the case of children failing their vision tests but this is particularly inappropriate at a time when the criteria for treatment is again being questioned.²²

The estimated cost of the doctor's time for these examinations is given in table 3, which shows the difference between the overall cost of joint health checks and nurse only checks of entrants is £55 per school per annum, a sum equivalent to barely two doctor sessions per annum per school. This saving would be appreciably less if, as is quite likely, an assistant school nurse was employed to help with a nurse only check. We have never doubted that nurse only health checks of entrants are cheaper than joint checks but as they are certainly less effective in revealing problems at least in this respect it is not true to say they are more cost effective.

Routine joint examinations of school entrants should be maintained

We believe that as society has decreed that for all its citizens 11 years of schooling be a compulsory experience, in their own right as young dependent citizens each and every child should be entitled to a health check on starting school. We are not alone in regarding this as necessary today as it was 80 years ago. The Court committee, whose philosophy at least is

widely accepted, was so strongly of this opinion as to advise that the medical examination of school entrants should again be made mandatory.²³ An independent, multidisciplinary committee charged with reviewing the child health services 10 years after Court has reaffirmed that every child 'round about the age of 5' should be seen by a doctor²⁴; this conclusion has been endorsed by the National Association of Head Teachers.²⁵

As we understand it, as health is dynamic, such a check does not mean a glance at a past opinion about a child's health scribbled on a preschool health record; as we all know, it is easy to make errors of commission in using ticks or crosses as well as of omission in routine procedures. Nor is it just an inquiry of what his parents may think presently about his health. A proper health check is an on the spot *verification* by a suitably qualified doctor or nurse acting on behalf of the child, that his physical state is satisfactory and that his functional development and his level of emotional development and social adjustment are appropriate for his age and personal circumstance. If these are so, it should be possible for the child to benefit to the full from enforced education in school; it also becomes possible to plan an individualised programme of subsequent health care in school.

At least half of all school entrants will be found to be physically and developmentally normal. This should be welcomed if one is truly in the business of preventive paediatrics; it is better to be doubly sure than uncertain or ignorant. There are some school doctors unfortunately who are avid for abnormality and regard confirmation of normal health and individual health education with mother and child as a waste of their time. However, most parents do not see it this way, though their views are often overlooked. For instance over 99% of the Paddington mothers attended their child's entrant examination¹²; and in a national inquiry a few years earlier 93% of parents interviewed thought medical examinations of schoolchildren were a good idea, a proportion that had not changed over the previous decade.²⁶

We do not think a system of selective medical examinations, such as that described by O'Callaghan and Colver,² is a reasonable alternative to routine examinations. It seems to us no more than an attempt to refine the identification of abnormality. It is arbitrary and exclusive rather than selective about whose *health* should actually *be checked*. Added to which it relies heavily on the concerns of parents and teachers, and on written records. Adult concern is not a foolproof pointer to childhood disorders; some of these do not necessarily cause concern to either parents or teachers, it depends on how observant they are, their expectation of what is normal, and their threshold of tolerance. Others may cause concern that may not be voiced even when this is invited, as in the case of mothers who are shy, lacking in confidence or inarticulate; but health care should be for all children, not just those whose parents are competent and caring.

As for preschool health records, in our

Paddington study we found on average just as many problems among children for whom there were records (1.28 per child) as among those without records (1.34 per child). Lucky the child who has no preschool health records: at least he will be seen by a doctor! We are reminded how 'at risk' registers were abandoned because a statistical likelihood of normality proved to be a poor guarantee that this would be found in a particular child whose name was not on the register. As the Warnock committee readily understood of educational difficulties, there is no substitute for informed and systematic observation of *all* children.²⁷

We realise of course that prevalence rates for disorders in school entrants vary widely, not only from health district to health district but from school to school (in our experience from 73 to 26%). Nevertheless, we do wonder how much of the striking differences between the rates in Paddington and in Cramlington, respectively 41 and 1.4%, with only one problem occurring in 73 of the latter children with no preschool records, may be accounted for by the different ways in which health checks were carried out, particularly the omission of neuro-developmental assessment of entrants in Cramlington. We deplore the current reductionist policy in service provision: if in doubt just cut it out. No prior study is mentioned by O'Callaghan and Colver of what might be missed by eliminating the medical role in routine health checks.

Another obvious reason might be the fact that a doctor had already examined many of the Cramlington entrants at the age of 4 to 4.5 years. We cannot see the need for such an examination unless it is clearly related to imminent admission to infant school. Under these circumstances it would be logical for the doctor to examine after entry only those children who were not known to have been examined during the previous 12 months. If one wants to describe this as selective examination we would not argue the point. As a matter of interest it was the neighbouring city of Newcastle upon Tyne that pioneered the use of routine medical examinations of children just before their entry to school.²⁸ We know of another 10 local education authorities that followed suit,²⁹ and the Court committee was readily convinced of their value both as a preventive child health care procedure and in establishing an integrated child health service involving general practitioners as general practitioners paediatricians in education medicine. As year after year slips by of disintegrated services this has become a pipe dream and interest in purposeful pre-entry school medical examinations has waned. They have usually been carried out in health service clinics, which have far better facilities for the examinations and save nurses' time while allowing them more scope,³⁰ but they have one serious disadvantage. The removal of the examinations from school premises reduces the medical presence in the school and makes mutual understanding, respect, and communication, and therefore cooperation between teachers and the school doctor and nurse much more difficult to achieve and maintain.

At least one can be sure that every child would be seen when nurse only checks are used but in discovering problems the nurse cannot go it alone. One in five of physical disorders might be missed and half of those associated with development. No service should be content to operate at a 73% effective level when it could knowingly do better, particularly if this also means greater customer convenience. One of the disadvantages of nurse only health checks is that the parents have to attend twice—unless (heaven forbid) the doctor has an annual 'balls and murmur' session without the parents being present—a very questionable practice. Even then one out of three of the parents would have to return for the doctor to sort out children with problems suspected by the nurse, a task normally carried out within the 20 minutes allotted on average to a routine medical examination.

The simple truth is that if only so much as a check of testes and heart has to be done and by the doctor—and no one has yet dared to suggest otherwise—the nurse only check becomes a joint check. The only question then is: which is the best way for doctor and nurse to share in the task of checking health? We would not want to be too dogmatic in answering this. Generally speaking, as the doctors have to do some of the physical examination it is sensible that they do it all; and they need to do the developmental testing, though as we have suggested some of this can be shared with the nurse. The nurses have traditionally taken measurements and tested vision and hearing and they do it very well. However, arrangements between doctor and nurse do have to be flexible. What suits one pair in one school may not be satisfactory in another school, nor suit another pair. Similarly, when they know their schools and catchment areas, and have learned that they can rely upon the information on preschool records, they should use their own discretion as to how comprehensive an examination they give a child to be satisfied about his health. This applies particularly to developmental assessment. The frequency with which individual children need to be seen again, and by whom, is always a matter of clinical opinion. This is universally understood and accepted in the case of children who have problems; to do otherwise would be to challenge the principle of clinical autonomy. Yet this is exactly what is done in the case of children who do not yet have problems! It is not the function of health authorities, nor of their more senior doctors and nurses, to lay down programmes of health checks indiscriminately for all children in all schools, and the division of labour between doctors and nurses. This is the responsibility of the doctor and nurse allocated to each school, and it is the only way in which properly individualised health care in school can be organised. It has also to be remembered that school doctors and nurses have a responsibility for the school as a community and not just for individual children.

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CURRENT TOPIC

Antimicrobial treatment for urinary tract infections

K Verrier Jones

The aims of treatment

One of the aims of treatment of urinary tract infection is to relieve distressing symptoms as quickly as possible. Another is to prevent recurrent infections in those children who experience frequently recurring symptomatic urinary tract infection. A third objective is to prevent infections in children who are deemed to be at greatest risk of developing reflux nephropathy or other forms of renal damage—that is, the very young child with vesicoureteric reflux. The management of urinary tract infection in childhood has been reviewed extensively by Jodal and Winberg,¹ McCracken,² and White.³

Before the start of treatment it is essential that the urine is examined microscopically and sent to the laboratory for culture, sensitivity, and colony counting. In infants suprapubic aspiration of urine under ultrasound control is the method of choice and where bag collection is used there will inevitably be a significant contamination rate with an appreciable number of false negative and false positive results leading in some cases to a delay in the onset of treatment and in others to unnecessary investigation. The risk of diagnostic error can be reduced by collecting two bag or clean catch samples and by the use of microscopy at the bedside. It is unacceptable to wait 48 hours for the results of culture and sensitivity before starting treatment in an infant or acutely symptomatic child. Paediatricians should become accustomed to making the diagnosis on the presence of white cells and organisms on direct microscopy of the unspun urine. As urinary tract infection in infancy rarely presents with symptoms localised to the urinary tract,⁴ and delay in treatment may result in permanent renal damage^{5,6} especially in the youngest children,⁷ every sick infant needs urgent urine examination.

While management of the acute or presenting urinary tract infection is relatively straightforward, the long term management of recurrent urinary tract infections, mainly in girls, and the use of prophylactic antibiotics for the prevention of reflux nephropathy is both complex and controversial. It is intimately connected with other aspects of long term management and investigation, and by the natural history and epidemiology of urinary tract infection.

Swedish data suggest that the commonest age for the first urinary tract infection is the first year of life⁸ and that the risk in childhood decreases thereafter. Although the incidence is higher in boys in the first month, by six months

urinary tract infections are more prominent in girls. Recurrent urinary tract infections occur in more than half the girls affected, but are uncommon in boys. Common host factors that predispose to renal damage are young age,⁹ vesicoureteric reflux,⁴ and delay in onset of treatment, although the presence of obstruction, neurogenic bladder, and stones are less common but equally important and potentially treatable. Bacterial virulence factors are also likely to influence the development of symptoms and reflux nephropathy.

Treatment of the acute infection

Treatment should be preceded by a thorough history and physical examination and special note made of urinary symptoms and recent antibiotic treatment. Examination should include an assessment of the child's general well being, degree of toxicity, and dehydration, if the child is acutely unwell, as well as the presence of a palpable bladder or kidneys and neurological signs in the lower limbs. In the acutely sick infant or child it is important to start to correct shock, dehydration, and electrolyte imbalance as soon as possible and antipyretics should be given to febrile children. In this acute situation the use of intravenous aminoglycosides is indicated and can be expected to result in a brisk clinical response, although the standard dose will need to be modified in those with acute or chronic impairment of renal function and levels monitored. Alternative, but less satisfactory, broad spectrum intravenous antibiotics are amoxycillin, the cephalosporins, amoxycillin and clavulanic acid in combinations (Augmentin, Beecham), azlocillin, and the aminoquinolones. The aminoquinolones are not generally recommended for children, however, and should be reserved for those cases where the more well tried antibiotics are ineffective, such as multiply resistant pseudomonas infections.¹⁰ In very severe and complicated infections intravenous treatment may be continued for five to 10 days, but more often the child is considerably better by 48 hours and a suitable oral antibiotic can be chosen according to the sensitivity reported by the laboratory. A one week course of oral treatment is usually sufficient and can be completed at home before changing to long term, low dose prophylaxis, which should be continued until investigation of the urinary tract has been completed, all the risk factors for development of reflux nephropathy have been

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assessed and long term management plans have been made.²

Most children, including some infants and children with systemic upset, will be only mildly unwell and able to tolerate oral fluids and oral antibiotics. Trimethoprim, amoxycillin, and clavulanic acid in combination are potent, effective broad spectrum antibiotics that give good results in most cases. Amoxycillin alone is likely to be effective against only 60–70% of *Escherichia coli* and cephalosporins are expensive and have not been as effective as other drugs in clinical trials. If the organism is sensitive to amoxycillin, however, this is an excellent and safe drug, which should be used in preference to the combination with clavulanic acid to reduce the risk of bacterial resistance to the newer drug. Five to seven days' treatment is effective in most cases and prolonged courses increase the risk of diarrhoea and thrush.

If there is no clinical improvement within 48 hours either the organism is not sensitive to the antibiotic chosen, or there is an underlying urological problem, such as obstruction. The antibiotic sensitivity should be reviewed, urgent ultrasound of the kidneys and urinary tract arranged and intravenous treatment considered if only oral treatment has been used so far. If obstruction is present a surgical opinion should be sought and drainage by a nephrostomy, or a suprapubic or bladder catheter, arranged as soon as possible.

In many children the symptoms of urinary tract infection are fairly trivial with symptoms largely confined to the lower urinary tract and little systemic upset. Even in this situation when the child is unlikely to require hospital admission there is no justification for a delay in treatment. Symptomatic lower urinary tract infections are generally associated with a significant increase in urinary white cells and can be easily diagnosed microscopically and subsequently confirmed on culture. In addition to the oral antimicrobial drugs already mentioned nalidixic acid and nitrofurantoin are excellent urinary antiseptics with a broad range of activity against Gram negative organisms. Good tissue concentrations are not achieved, however, and they should not be used in systemically ill children or in those in whom acute pyelonephritis is suspected or in children with renal failure.

Prophylaxis

Prophylactic treatment is the use of a drug in a high risk situation to reduce the chance of subsequent infection. It is the duty of the paediatrician to anticipate those situations where this may be of value and ensure that appropriate treatment is given. Catheterisation of the urinary tract for any reason carries a high risk of introducing bacteria at the time of the procedure.¹¹ In paediatric wards this occurs most commonly at the time of a micturating cystogram and unless prophylaxis is given routinely in this situation, the children who are most at risk of acquired renal damage will be put at increased risk by this procedure. Our policy is to give trimethoprim in full dosage for 48 hours from the time of catheterisation. Children who

are undergoing urological instrumentation of the urinary tract receive a single intravenous injection of an aminoglycoside in full dosage, whatever their level of renal function. Before and during elective surgery on the infected urinary tract a full course of an appropriate antibiotic, usually an aminoglycoside or azlocillin or ciprofloxacin, is used to reduce the risk of Gram negative septicaemia. This is because a child with an abnormal urinary tract who has had several courses of treatment previously is likely to have multiply resistant organisms including proteus and pseudomonas, and close cooperation with a microbiologist is essential.

It is now clear that approximately 50% of infants born into families where a first degree relative has vesicoureteric reflux or reflux nephropathy also have vesicoureteric reflux themselves, although in most it is grade I or II (Medical Research Council grading).¹² In this group of infants, neither the natural history nor the benefits and risks of prophylaxis or other modes of intervention have been evaluated. Clearly this group of infants poses new questions on the role of prophylactic treatment in relation to sterile vesicoureteric reflux and the prevention of reflux nephropathy as do those children with vesicoureteric reflux detected as a result of antenatal ultrasound examination.¹³

Most often prophylaxis is used to prevent reinfection after the first, presenting infection, because there is deemed to be an appreciable risk of progressive renal damage, which occurs mainly in children under 5 years of age with vesicoureteric reflux. The development of reflux nephropathy after the age of 5 is relatively uncommon, although some cases have been reported, mainly when severe vesicoureteric reflux has been present and there has been a delay in the onset of treatment.¹⁴ In some groups of children with established reflux nephropathy who have been followed for prolonged periods new scars have developed in a minority whether or not long term low dose prophylaxis has been used.^{15 16} The value of prolonged treatment in teenage girls is in doubt, unless they have frequently recurring symptoms which cannot be managed by other means. The risk of pregnancy increases significantly after 16 and it is theoretically undesirable for these girls to conceive while taking medication of doubtful value, particularly folate antagonists such as trimethoprim. In reality teenage girls are poorly motivated to take prophylaxis unless they have had very troublesome symptoms and prefer short courses of treatment when their symptoms flare up.

The drugs that have been shown to be effective in preventing reinfection are nitrofurantoin¹⁷ and trimethoprim.¹⁸ They are both used in doses of 1–2 mg/kg/day given usually as a nightly bolus; this is well below the normal therapeutic dose. Side effects have been relatively uncommon with both these drugs, but recently there has been some anxiety about the small risk of pulmonary and hepatic fibrosis in children taking nitrofurantoin for prolonged periods.¹⁹ Amoxycillin, cephalosporins, and nalidixic acid are relatively ineffective as prophylactic agents probably because the bowel

soon becomes colonised with *E coli* resistant to the drug taken.²⁰ Reinfection of the urinary tract, when it occurs, is likely to be with a resistant organism. Co-trimoxazole is also effective as a prophylactic agent but the greater risk of side effects and complications from the sulphamethoxazole component of this trimethoprim combination have led to a reduction in the use of this drug in the long term management of urinary tract infection in childhood.²¹

Single dose and short course treatment

Single dose treatment and very short course treatment is attractive because it is associated with improved compliance and reduced side effects and cost, and it was used successfully in adolescent girls by Fine and Jacobson.²² There is evidence to suggest that those who have an early recurrence of infection may have upper tract infection or underlying abnormality. It has been suggested in adults that single dose treatment could be used as a method of screening for those who need further investigation.

In a randomised controlled study in children and adults Bailey and Abbott showed that the cure rate after a single dose of amoxycillin was as effective as a one week course.²³ Others, however, have found that early recurrence after 10 days was more likely to occur after single dose treatment than a one week course, although most recurrences were asymptomatic.²⁴ It would be prudent therefore to use single dose treatment in girls over 5 years of age with grossly normal urinary tracts in whom the risk of progressive damage is minimal, but to treat younger children and those with abnormal urinary tracts, systemic, or upper tract symptoms with longer courses.

When not to treat

There are now a number of long term follow up studies in schoolgirls with asymptomatic bacteriuria that show that this is a benign condition in girls with radiologically normal kidneys over 4 years of age even if vesicoureteric reflux is present.^{15 16} Reflux nephropathy once established progresses very slowly in a small proportion of cases and usually when vesicoureteric reflux is present and reinfection occurs. There is no clear evidence that long term low dose prophylaxis is superior to no treatment in asymptomatic children, however, as reinfection with new organisms may be more damaging to the kidney than continuous infection with an organism of low pathogenicity.²⁵ In girls the natural history is for reinfection to occur in a high proportion after treatment has been discontinued. Conventional courses of treatment are doomed to failure in a large proportion of girls, therefore, and long term low dose prophylaxis is less successful in asymptomatic infection because of poor compliance and lack of motivation. In boys conventional courses may be used effectively as reinfection is rarely a problem except in the grossly abnormal urinary tract.

The grossly abnormal urinary tract

Recurrent asymptomatic infection is relatively

common in children with neurogenic bladders or where there is gross dilatation or stasis of the urinary tract, a ureterostomy, after bladder reconstruction, or renal calculi, and in those children using self intermittent catheterisation. It is usual to treat the infection when it first comes to medical attention, particularly in children under 2 years, but infections that recur after three or four courses of appropriate antibiotic treatment in the absence of appreciable symptoms are likely to continue to recur after further courses. The organisms may become increasingly difficult to treat, however, because of acquired antibiotic resistance. It is important to ensure that proper surgical management has been carried out—for example, removal of all urinary calculi, relief of obstruction, and proper management of the neurogenic bladder. Although prophylaxis is helpful in some cases, repeated breakthrough infections often become a problem in these children. In this situation it is best to leave the infection untreated unless symptoms become troublesome or surgery is planned. The child can then be given a five to 10 day course of appropriate treatment, until there is clinical improvement, or surgery has been completed. The choice of antibiotic may be difficult and these children with multiply resistant organisms such as proteus, pseudomonas, and *E coli* usually require treatment with expensive newer intravenous antibiotics rather than first line drugs.

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NEONATOLOGY—THEN AND NOW

Plasma volume changes in the newborn (1958/59)

The fluid shift from the vascular compartment immediately after birth

DOUGLAS GAIRDNER, JOHN MARKS, JANET D ROSCOE, R O BRETTELL

Cambridge Maternity Hospital (Arch Dis Child 1958;33:489-98).

Postnatal plasma shift in premature infants

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In 1952, Gairdner and his colleagues drew attention to the fact that there was a consistent rise in the haemoglobin of the newborn immediately after birth. Later they went on to challenge the theory current at the time that this rise was due to transfer of blood from the placenta and the summary of the first of these papers begins:

'Immediately after birth there is a rise in concentration of haemoglobin and PCV [packed cell volume] in the majority of infants. The rise may be discernable within a few minutes of birth and is probably completed within an hour or two. It occurs in the absence of any transfer of placental blood'.

The conclusion reached was that these changes were due to a shift of fluid from the intravascular space:

'... mainly whole plasma and its volume may amount to a large fraction of the circulating plasma at birth, a quarter or more. In addition there is a shift of fluid from the red cells, the volume of red cells contracting after birth by an average of 3%. . . . These results imply that the foetus in utero is hydraemic, i.e. has a large plasma volume'.

The second paper confirms that a similar plasma shift occurs in preterm infants and while:

'in this series the magnitude of the postnatal plasma shift bears no relation to the development of respiratory distress. . . .'

'It was suggested that the shift might take place particularly from the pulmonary circulation and so contribute to the development of pulmonary oedema and respiratory failure'

Today. What to do, if anything, about the changes in haemoglobin, packed cell volume, plasma, and whole blood volume in the first day or two of life has exercised the minds of paediatricians for at least 30 years. These early observations have stood the test of time and it is now generally accepted that transfusion of extra blood from the placenta, once actively encouraged, can be harmful. It initially renders the baby hypervolaemic, encourages dilatation of the capillary bed with further transudate, which causes increased oedema and intravascular polycythaemia. It is also accepted that transudation from the pulmonary capillary is a precursor of hyaline membrane formation so retention of plasma within the vascular space would seem a sensible objective. The fact that an early diuresis signals a good prognosis in preterm infants with respiratory distress probably indicates return of this oedema fluid into the intravascular space with the associated improved haemodynamics similar to that seen after haemodilution, the therapeutic equivalent in infants with hyperviscosity.

I have always felt that the advantages of improved oncotic pressure (albeit transient) from infusions of albumin with the consequent reduction of tissue oedema and improved renal output outweigh any disadvantage there might be in increasing blood volume and so possibly prolonging patency of the ductus arteriosus. The fact that oedema does not correlate well with serum albumin is not the point.¹ Whether the baby benefits from its administration surely is and recent work would encourage the practice of infusion of salt free albumin.²

¹ Cartledge PHT, Rutter N. Serum albumin concentrations and oedema in the newborn. *Arch Dis Child* 1986;61:657-60.

² Greenough A, Greenall F, Gamsu HR. Immediate effects of albumin infusion in ill preterm neonates. *Arch Dis Child* 1988;63:307-8.

Douglas Gairdner won a scholarship to Oxford before transferring to medicine at the Middlesex Hospital, London, graduating in 1936. After a fellowship at Bellevue Hospital, New York, he served with the Royal Army Medical Corps in the Middle East. After the war he was appointed assistant to Professor Sir James Spence in Newcastle before moving to Cambridge in 1947. His contributions to paediatric research and literature, which his modesty prevents him from enumerating, are too extensive to detail. His approach is exemplified, however, when he says of neonatal research 'It was a joy for us that the extremely simple technology, which was all we had, was yet capable of yielding worthwhile results' and he praises the dedication of his hard working

colleagues. He was one of the many paediatricians of the day who rejoiced in the elevation of babies from being something of second class citizens to fully accepted 'patients' in their own right.

Douglas Gairdner has served all aspects of paediatrics with great distinction and is possibly best known for his 15 years Co-Editorship of the *Archives of Disease in Childhood* and Editorship of the first four editions of *Recent Advances in Paediatrics*. The BPA recognised his many contributions in awarding him the Spence Medal (1976) and electing him to Honorary Membership (1977).

C H M WALKER

LETTERS TO THE EDITOR

Mechanical ventilation and respiratory syncytial virus infection

SIR,—Drs Lebel *et al* report weight and prematurity as risk indicators for the need for ventilation in bronchiolitis.¹ In their case-control study a viral cause was determined in only 32%; infants with underlying cardiopulmonary abnormalities—who are known to be at increased risk for severe respiratory syncytial virus infections and mortality^{2,3}—were excluded. Thus the results from their study may not readily be applied to all infants with bronchiolitis who need hospitalisation.

We would like to present the preliminary results of a prospective study (1987–9) of children admitted with a respiratory syncytial virus infection to the Sophia Children's Hospital, The Netherlands. In all patients the infection was proved by direct immunofluorescent assay. Nineteen patients needed mechanical ventilation and 82 were admitted to the general ward.

Weight and age (corrected for prematurity) on admission were significantly related with mechanical ventilation (by χ^2 , $p < 0.05$). No relation between mechanical ventilation and risk factors for severe respiratory syncytial virus infections (prematurity, congenital heart disease, bronchopulmonary dysplasia, or immunodeficiency states) was found. Nine (47%) of the ventilated patients and 36 (43%) of the non-ventilated patients belonged to the risk group. In a stepwise logistic regression analysis (while controlling for the covariates: age, prematurity, and risk factors for severe respiratory syncytial virus infection) only weight appeared to be significantly related to

the need for mechanical ventilation (coefficient -0.36682 (SE 0.1685), $p = 0.01$), while none of the other variables did. Prematurity and age were not independent risk indicators for mechanical ventilation in this study. In contrast to Lebel *et al*, who report odds ratios as 'relative risk', from the data of our prospective study we are able to estimate the absolute risk of mechanical ventilation related to the weight on admission (figure). A low weight is related to an increased risk for mechanical ventilation. For infants less than 5000 g, a relative risk for mechanical ventilation of 4.3 (95% confidence interval 1.3 to 13.9) was estimated.

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Helicobacter pylori and protein losing enteropathy

SIR,—We have demonstrated a high prevalence of anti-*Helicobacter pylori* (formerly *Campylobacter pylori*) antibodies in children under the age of 3 years in The Gambia, West Africa.¹ Using a serological test validated by histology and microbiology, 41/77 (53%) of children with chronic diarrhoea were shown to have significantly high anti-*H. pylori* IgG antibody titres, and indeed, the prevalence of *H. pylori* antibodies in healthy asymptomatic children of the same age was also high at 26%.

It was against the background of these findings that we were interested in the description, in 1987, by Hill and colleagues, of transient protein losing enteropathy in association with acute infection with *H. pylori*.² This observation might be due to chance but could have important consequences in the nutritional rehabilitation of infants with chronic diarrhoea and severe protein energy malnutrition.

Therefore we undertook a study to establish whether or not *H. pylori* infection was associated with protein losing enteropathy in Gambian children with chronic diarrhoea.

Fifty three subjects (25 boys, 28 girls; mean age 19 months) were studied and all had chronic diarrhoea (more than three loose stools per day for more than two weeks) and severe protein energy malnutrition (32 marasmus, 21 marasmic-kwashiorkor).

After admission, three consecutive fresh stool samples were collected for virological, parasitological, and bacteriological investigation. Specific anti-*H. pylori* IgG antibody was measured by enzyme linked immunoabsorbent assay (ELISA) in all subjects. Gastroscopy and antral mucosal biopsy were performed in 20/53 children.

Protein losing enteropathy was estimated by random faecal α_1 -antitrypsin measurement. Whole single stools were collected ensuring that both the liquid and solid phase were obtained. These were frozen and lyophilised and α_1 -antitrypsin measured by a single radial immunodiffusion method. Random faecal α_1 -antitrypsin measurement (normal mean (SD) value in healthy Gambian children = 1.54 (0.23) mg/g stool) has been shown to be a reproducible screening test for excessive enteric protein loss and has been validated against $^{51}\text{chromium}$ labelled albumin excretion in the stool.³

Fifty six percent of this group of children had significantly raised anti-*H. pylori* antibody titres and in 11/20 gastroscopied this was associated with recovery of the organism and histological gastritis. *Strongyloides stercoralis*, and *Giardia lamblia* were found in 11 and 38% of the patients respectively. Hypoalbuminaemia occurring in children with *S. stercoralis* was found to be associated ($r = 0.952$, $p < 0.001$) with increased faecal α_1 -antitrypsin excretion (mean (SEM) = 2.47 (0.9) mg/g stool) whereas there was no difference between levels of faecal α_1 -antitrypsin found in children with (1.57 (0.2) mg/g stool) or without (1.62 (0.3) mg/g stool) evidence of *H. pylori* infection.

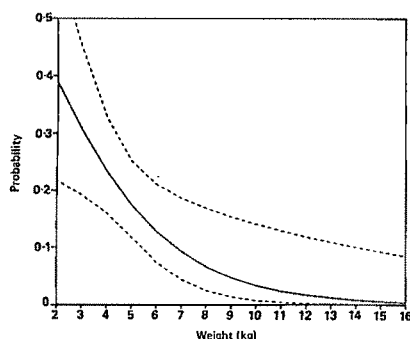
Therefore, in this study we failed to show that chronic infection with *H. pylori* is associated with protein losing enteropathy.

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- 1 Sullivan PB, Thomas JE, Wight DGD, *et al*. *Helicobacter pylori* in Gambian children with



Probability of need for mechanical ventilation. Dotted lines show 90% confidence interval based on logistic model.

chronic diarrhoea and malnutrition. *Arch Dis Child* 1990;65:189-91.

- 2 Hill ID, Sinclair-Smith C, Lastovica AJ, et al. Transient protein losing enteropathy associated with acute gastritis and *Campylobacter pylori*. *Arch Dis Child* 1987;62:1215-9.
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Monitoring treatment in congenital adrenal hyperplasia

SIR,—Appan *et al* are to be congratulated on achieving normal growth in so many of their patients with congenital adrenal hyperplasia.¹ I would not wish paediatricians to conclude, however, that the management of this condition merely requires a standard dose of glucocorticoid and mineralocorticoid calculated from surface area to be chosen at birth and growth monitored thereafter until adulthood. The decision to adjust treatment on the basis of an abnormal change in growth velocity or skeletal maturation is inevitably a retrospective one. The authors concede that an advanced bone age can rarely be recovered. Why not try to predict such an occurrence before it is too late?

The biochemical indices to monitor control are by no means entirely reliable alone. They are certainly useful to detect problems with treatment compliance, particularly plasma testosterone values which are less influenced by good short term compliance. Appan *et al* conclude their paper by stating that frequent adjustment of medication is needed during periods of rapid growth in infancy and puberty. Periods of short term monitoring of biochemical indices along the lines recently recommended,² together with the use of standard auxological techniques in the longer term, is surely a sensible way to achieve this.

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- 1 Appan S, Hindmarsh PC, Brook CGD. Monitoring treatment in congenital adrenal hyperplasia. *Arch Dis Child* 1989;64:1235-9.
- 2 Hughes IA. Management of congenital adrenal hyperplasia. *Arch Dis Child* 1988;63:1399-404.

Herpes simplex infections in atopic eczema

SIR,—Patients with atopic eczema have an increased susceptibility to cutaneous viral infections, including herpes simplex, common warts, vaccinia, and molluscum contagiosum. This is thought to be due partly to a mild but definite depression of T cell function.¹

I was struck, however, by the apparent high incidence of the herpes simplex infection in children admitted to the Birmingham Children's Hospital with an acute exacerbation of atopic eczema. To test my observations, I did a retrospective study to find this incidence in those admitted over a period of two years and a prospective study over a period of one year.

Swabs were taken if herpes simplex was clinically suspected—that is, there were vesicles or pustules in a child with atopic eczema. The presence of the herpes simplex virus was tested by indirect immunofluorescence and cytopathic changes on tissue culture.

During the retrospective two year period, 10 out of 119 children were confirmed to have a herpes simplex skin infection. The prospective study, over a period of one year, showed eight out of 74 children with atopic eczema to

have a confirmed herpes simplex skin swab. Thus during the combined three year period, the incidence of the virus was approximately 10%. Two children had one recurrence and one child had two recurrences.

All children confirmed to have a herpes simplex skin infection improved after seven to 10 days even though two, initially, had developed severe systemic upset. They were all treated with a five day course of oral acyclovir. Herpes simplex was confirmed in all children who were clinically suspected of having the virus, reflecting the ease of diagnosis and of culture of the virus. The incidence of about 10% of herpes simplex infection in acutely exacerbated atopic eczema was also found by David and Longson.² This incidence may have been an underestimate as swabs were only taken on clinical suspicion that the virus was present. There may have been similar underestimations in our study. When infected eczema fails to respond to antibiotics within two days this is thought to suggest a herpes simplex infection.² It would be interesting to determine the incidence of the herpes simplex virus in acute eczema when it is not clinically obvious.

This study confirms my observation of the high incidence of herpes simplex in atopic eczema. It should always be considered in an acute exacerbation of atopic eczema as it can cause considerable associated systemic disease.

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- 1 Carapeto FJ, Winkelmann RK, Jordan RT. T and B lymphocytes in contact and atopic dermatitis. *Arch Dermatol* 1976;112:1095-100.
- 2 David TJ, Longson M. Herpes simplex infections in atopic eczema. *Arch Dis Child* 1985; 60:338-43.

Self management plans for asthma

SIR,—Comics and booklets, training courses for patients, asthma nurses—do they help to reduce morbidity in asthma? The evidence is at worst negative and at best contradictory. A consensus is emerging that self management is the key to good control and that a clearly written set of instructions—a self management plan—is the means to achieve this goal.

The article by Fletcher *et al* suggests that clear advice might have helped to prevent some deaths from asthma.¹ Two recent articles from *Thorax* come to similar conclusions.

Sibbald concluded that psychological factors were not major determinants of the responses of her adult asthmatic subjects to two hypothetical attacks of asthma.² Simple messages, teaching patients how to cope rather than trying to improve their knowledge of disease, would be most likely to reduce morbidity. A self management scheme of this type was assessed in an open study by Beasley and colleagues.³ A written plan and a peak flow meter were provided for each of the subjects. Patients improved over a seven month period, suggesting that the plan was successful. A controlled study, with an assessment of the (non-standard) advice given and an analysis of the important features which were responsible for improved control, will be essential sequels to this study.

Of immediate practical help, the National Asthma Campaign has recently introduced two children's asthma cards, based largely on a similar design used successfully at

Hammersmith Hospital for over 10 years.⁴ One card is for personal use by parents or child. The other is to be taken to school. There are sections for regular treatment, relief treatment, and emergency management. Brief guidelines are printed for the emergency doctor and for the parents or school teachers.

The cards are available at no charge from The National Asthma Campaign, 300 Upper Street, London N1 2XX. I urge you to use them.

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- 1 Fletcher HJ, Ibrahim SA, Speight N. Survey of asthma deaths in the Northern region, 1970-85. *Arch Dis Child* 1990;65:163-7.
- 2 Sibbald B. Patient self care in acute asthma. *Thorax* 1989;44:97-101.
- 3 Beasley R, Cusley M, Holgate ST. A self management plan in the treatment of adult asthma. *Thorax* 1989;44:200-4.
- 4 Silverman M. *Asthma in childhood*. London: Current Medical Literature, 1985.

Effect of fever on recurrence rate of febrile convulsions

SIR,—The paper by Drs El-Radhi and Banajeh may be criticised on the grounds that they have combined data from retrospective and prospective studies for joint analysis.¹ Even if their results were to be accepted at face value, I suspect that they have drawn the wrong conclusion from their data. Rather than suggesting that the height of the initial fever provides stimulation of non-specific immunity, thereby reducing the chance of future infections (are we therefore misguided in trying to lower fever?), it is surely more reasonable to interpret their data by assuming that there is natural variability in the temperature threshold required for convulsion. Any individual may convulse if the temperature rises high enough, as in heat stroke, and as the incidence of febrile convulsion decreases with age, cerebral maturation appears to be associated with increase in temperature threshold required for convulsion. Their groups are clearly self selecting: those infants convulsing with temperatures below 39°C have a low temperature threshold and would be expected to have more attacks, as more infections cause pyrexias of 38-39°C than 40-41°C. Those requiring temperatures above 40°C will have less, both because high pyrexia is less common, and because their convulsion threshold will increase naturally with age to levels above those caused by infectious illness.

Perhaps we should be directing our attention to those infants who present with convulsion associated with low grade fever. Simple methods of fever control are less likely to prevent a pyrexia of 38.5°C than one of 40-41°C, and it may be appropriate to consider early introduction of anticonvulsant treatment in this group. This could be withdrawn after a relatively short period of six months to one year, as the infant's convulsion threshold may well have risen to levels where fever control alone is adequate.

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- 1 El-Radhi AS, Banajeh S. Effect of fever on recurrence rate of febrile convulsions. *Arch Dis Child* 1989;64:869-70.

Dr El-Radhi comments:

I accept the first criticism that about half of the 154 patients in our study were studied retrospectively. Currently we are carrying out a new study in which patients are only prospectively studied.

I agree with the second comment that we are perhaps misguided in believing that lowering the fever in a child is good practice. Accumulated data from the past 20 years suggest that fever may be beneficial to the infected host.¹ In febrile convulsion, infection with virus plays a major part. Could the child then become 'neuro-immune' around the age of 5 years rather than the currently held notion of cerebral maturation? More research is needed to determine the role of interleukin I in astrocytes.²

We, too, believe firmly that each child has his own threshold for eliciting a convulsion and that the higher the threshold the greater the fever required to trigger a convulsion. In other words, the child's threshold can be determined by the degree of temperature at the time of the fit.

The group of children with the lowest fever (38–38.9°C) who experience more recurrences, should be of interest for follow up for a longer period because in this group we may find the reported increased incidence of epilepsy after a febrile convulsion.³ Although it may be appropriate to consider anticonvulsant prophylaxis here, such prophylaxis appears to be more controversial now than a decade ago.

1 Kluger MJ. Fever. *Pediatrics* 1980;66:720–4.

2 Atkins E. Fever—new perspectives on an old phenomenon. *N Engl J Med* 1983;308:958–60.

3 Nelson KB, Ellenberg JH. Prognosis in children with febrile seizures. *Pediatrics* 1978;61:720–7.

Growth hormone deficiency in children with chromosomal abnormalities

SIR,—We were intrigued by a recent report of Abusrewil *et al.*¹ They described a boy with a ring 18 chromosome karyotype and complete growth hormone deficiency responsive to treatment. We are following up two patients with chromosomal deletions who have also responded favourably to growth hormone treatment.

Case 1, a boy, was born at 36 weeks' gestation weighing 1960 g. He had microcephaly and multiple malformations, including dysplastic right kidney, thoracic hemivertebra, pulmonary stenosis, hernias, and hypospadias. Karyotype was male with partial ring 21 chromosome and partial monosomy 21. Holoprosencephaly was seen on a computed tomogram of the brain. Similar cases with a broad phenotypic spectrum have been described before.^{2–3} At 3.9 years of age he was severely retarded, his length was 83.4 cm (–4.5 SD score), weight 10.7 kg, and bone age 18 months. Maximum stimulated growth hormone concentrations were 5.6 mIU/l and 1.4 mIU/l in the levodopa and clonidine test, respectively. Thyroxine concentration was normal. Growth hormone treatment with somatrem (Protropin) at a dose of 1.25 mg subcutaneously three times a week was started and has been continued for 16 months now. Growth velocity increased from 3.4 cm/year pretreatment to 9.5 cm/year during treatment.

Case 2, a girl, was born at term weighing 2070 g. She had microcephaly, downward

slanted palpebral fissures, long hands with a proximal thumb, cleft soft palate and bilateral atresia of the ear canals. Primary hypothyroidism was diagnosed at age 7 years, but the growth rate did not improve much on treatment. At 11.4 years, she was only mildly mentally retarded, height was 121.5 cm (–3.23 SD score), weight 21.3 kg, and bone age 8.8 years. Maximum growth hormone concentrations were 15.2 mIU/l in a clonidine test and 21.4 mIU/l in an insulin stimulation test, and 8.4 mIU/l in a 12 hour overnight study. Chromosome analysis showed deletion of the long arm of chromosome 18.⁴ A computed tomogram of the brain was normal. On treatment with somatrem 2.5 mg subcutaneously three times a week for one full year height velocity improved from 3.6 cm/year to 6.7 cm/year. Growth hormone treatment was then stopped for eight months with a decrease in height velocity to 5.0 cm/year. For the past six months, the patient has received somatrem 1.25 mg subcutaneously daily and has grown at a rate of 8.25 cm/year.

It is remarkable that our patient with ring 21 chromosome abnormality also has growth hormone deficiency, like the patient of Abusrewil *et al.* and two further patients they cite from the literature who all had a ring 18 chromosome karyotype.¹ We agree that poor growth and short stature is a hallmark of many chromosomal disorders, but may occasionally be associated with growth hormone deficiency and needs to be diagnosed.

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1 Abusrewil SS, McDermott A, Savage DCL. Growth hormone, suspected gonadotrophin deficiency, and ring 18 chromosome. *Arch Dis Child* 1988;63:1090–1.

2 Aronson DC, Jansweijer MC, Hoovers JM, Barth PG. A male infant with holoprosencephaly, associated with ring chromosome 21. *Clin Genet* 1987;31:48–52.

3 Gardner RJ, Monk NA, Clarkson JE, Allen GJ. Ring 21 chromosome: the mild end of the phenotypic spectrum. *Clin Genet* 1986;30:466–70.

4 Wertelecki W, Gerald PS. Clinical and chromosomal studies in the 18q[–] syndrome. *J Pediatr* 1971;78:44–52.

Generalised lymphangiomatosis with chylothorax

SIR,—We read with interest the article by Dunkelman *et al.*¹ and would like to add a description of an infant with lymphangiomatous scalp lesions currently under our care. A 25 year old pregnant woman with two previous first trimester miscarriages was noted at 27 weeks' gestation to have polyhydramnios. Ultrasound scan of the fetus showed pleural and pericardial effusions, ascites, and multiloculated fluid filled scalp lesions. The mother was blood group O negative and had irregular antibodies, although these were considered unlikely to cause haemolysis. At 33 weeks' gestation spontaneous labour resulted in delivery of an hydropic infant boy weighing 2325 g. The scalp lesions were bilateral, symmetrical, and localised to the parietal region. They were up to 1.5 cm in diameter and similar in appearance to a bunch of grapes (figure). There was no obvious communication



Localised scalp lesions.

to other structures, aspiration yielding clear fluid. A biopsy specimen showed lymphangioma circumscriptum.

The baby had bilateral pleural effusions aspirated and was initially ventilated for four days. Investigation failed to demonstrate any cause for the hydrops. Full skeletal survey showed no limb reduction or lytic lesions, only asymmetry of the thoracic cage. Aspiration of a small left pleural effusion at 1 week of age yielded clear fluid with numerous lymphocytes on microscopy. Subsequent chest radiography was consistent with pulmonary lymphangiectasia and computed tomography of the chest at 1 month revealed interstitial thickening consistent with this diagnosis. Lung biopsy has not been performed. Chronic ventilator and oxygen dependence ensued before final successful extubation after 10 weeks. Enteral feeding was commenced at 1 month with small volumes of Pregestimil (Bristol-Myers).

Subsequently a symptomatic left pleural effusion has required thoracentesis on five occasions, with the most recent specimen yielding a turbid fluid identifiable as chyle (protein 41 g/l and triglyceride 4.14 mmol/l) with abundant white cells, all lymphocytes. The infant is now 4 months of age and while remaining oxygen dependent is completely enterally fed with no symptoms attributable to lymphangiomatous bowel involvement. The scalp lesions have not increased in size and are now epithelialising.

Generalised lymphatic abnormalities are recognised causes of hydrops fetalis.² We are not, however, aware of any previous reports of an association between lymphangiomatous scalp lesions and chylothorax, which in this case presented antenatally.

1 Dunkelman H, Sharif N, Berman L, Ninan T. Generalised lymphangiomatosis with chylothorax. *Arch Dis Child* 1989;64:1058–60.

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Salicylate poisoning in dermatological treatment

SIR,—We read with interest the article on the successful treatment of a harlequin fetus.¹ We note that the baby was initially treated with topical liquid paraffin containing 1% salicylic acid every three hours. This resulted in significant percutaneous salicylate absorption and systemic toxic manifestations. We have had similar problems with salicylate toxicity after the topical application of salicylate containing preparations for the management of skin disorders in two children.

One was an infant born at 38 weeks' gestation and weighing 2500 g. His skin was covered by a collodion like membrane which within 24 hours started to crack and peel in large plaques. Topical 2% salicylic acid in aqueous cream was applied every three to four hours. On day 3 the baby vomited feeds and had a persistent metabolic acidosis. His salicylate concentration was 3.1 mmol/l. Topical salicylate treatment was stopped and a high fluid intake ensured by intravenous administration. He made a complete recovery.

The second patient was a 12 year old boy with severe ichthyosis. Treatment was started with topical 2% salicylic acid in simple cream applied to the whole body twice daily. The salicylate concentration was increased to 5% on day 3 of treatment and 10% on day 5. On day 8 he developed symptoms of salicylate toxicity. His blood salicylate concentration was 3.3 mmol/l. Topical salicylate treatment was stopped. Intravenous fluids and bicarbonate were given and complete clinical and biochemical recovery was achieved after two days.

Topical salicylate acid in paraffin or simple cream is suggested by several authors as treatment in a number of skin disorders.²⁻⁴ Our two cases and the one described by Ward and Jones¹ show that significant percutaneous salicylate absorption can occur not only in newborn infants but also in older children, especially when salicylate preparations of increasing strength are used. We suggest that all topical salicylate treatment should be routinely monitored with salicylate blood concentrations especially during the initial few days after onset or after any changes in treatment.

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1 Ward PS, Jones RD. Successful treatment of a harlequin fetus. *Arch Dis Child* 1989;64:1309-10.

2 Robertson NRC. *Textbook of neonatology*. Edinburgh: Churchill Livingstone, 1986.

3 Forfar JO, Arneil GC. *Textbook of paediatrics*. Edinburgh: Churchill Livingstone, 1984.

4 Avery GB. *Neonatology*. Philadelphia: JB Lippincott, 1981.

Lichen sclerosis

SIR,—In response to the article on lichen sclerosis by Dr Berth-Jones *et al*, I would like to take them to task on their quoting 'that there is absolutely no evidence to support any link between lichen sclerosis and sexual abuse'.¹ I disagree that the chances of these two problems occurring together would seem very remote. I have under my care over 400 cases of lichen sclerosis and am well versed in the appearance of lichen sclerosis lesions at sites of trauma—for example, where waist bands and bra straps cause friction. What is

more, some patients report extra genital lesions occurring at sites of trauma—for example, oven burns.

It is my feeling that vulval trauma may precipitate vulval lichen sclerosis. I have seen two cases, a girl aged 4 and another aged 6, with definite lichen sclerosis of the vulva and they have also been sexually abused. Another 8 year old girl with a five year history of anogenital lichen sclerosis had also probably been sexually abused at the age of 3.

It is therefore important to accept that lichen sclerosis does occur at sites of trauma and that the trauma may be sexual abuse.

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1 Berth-Jones J, Graham-Brown RAC, Burns DA. Lichen sclerosis. *Arch Dis Child* 1989;64:1204-6.

Drs Berth-Jones, Graham-Brown, and Burns comment:

We are most grateful for Dr Harrington's comments and her important observations. We should be extremely interested to see her patients reported in more detail as they would then be the first properly documented cases in which lichen sclerosis has been found in association with established childhood sexual abuse. In contrast, there are numerous reported examples of lichen sclerosis being misdiagnosed as abuse. In addition to the cases we referred to in our article, it would seem possible that another example occurred in 1987 in Cleveland.¹ Yet another was reported recently by Jenny *et al*.²

The presence of lichen sclerosis does not exclude the possibility of coincidental sexual abuse, but we were concerned to emphasise that misdiagnosis of lichen sclerosis as sexual abuse is not an uncommon phenomenon.

1 Butler-Sloss E. *Report of the inquiry into child abuse in Cleveland 1987*. London: HMSO, 1988:134.

2 Jenny C, Kirby P, Fuquay D. Genital lichen sclerosis mistaken for child sexual abuse. *Pediatrics* 1989;83:597-9.

Lichen sclerosis and sexual abuse

SIR,—Dr Berth-Jones *et al* refer to the potential for misdiagnosis of severe anogenital lichen sclerosis as sexual abuse.¹ They state that 'there is absolutely no evidence to support any link between lichen sclerosis and sexual abuse' and the 'chances of these two problems occurring together would seem very remote indeed'. We wish to report such a case.

We have treated 20 girls aged 4-11 years with lichen sclerosis over a two and a half year period. One girl, aged 7.5 years, presented with a four month history of intense diurnal frequency of micturition and wetting, and a sore vulva. The appearances were suggestive of early lichen sclerosis with patchy pallor and inflammation, plus minor fusion of the labia minora. Subsequently the changes became much more marked with characteristic thickened sclerotic white plaques, wrinkling, areas of acute inflammation, excoriation, and purpura. Substantial improvement has occurred with topical clobetasone. There have, however, been psychological problems and concern about possible abuse has persisted.

The girl has a complex social background, her stepfather being a schedule I offender (physical injury in a different family). Careful social and psychological investigation initially failed to support a diagnosis of abuse. Over the next year, coincident with worsening of her lichen sclerosis, she developed frequent encopresis, not associated with faecal retention.

She eventually disclosed sexual abuse by her stepfather and much of her story was validated independently by her young brother.

A diagnosis of lichen sclerosis does not exclude sexual abuse, the diagnosis of which, as always, depends more upon statements by the child than upon physical findings. There is the additional possibility that chronic trauma in the presence of low grade skin infection may on occasion lead to the changes of lichen sclerosis.

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1 Berth-Jones J, Graham-Brown RAC, Burns DA. Lichen sclerosis. *Arch Dis Child* 1989;64:1204-6.

Fragile X mental retardation

SIR,—It is not only in the context of mental retardation without dysmorphic features that the general paediatrician should consider fragile X syndrome.¹ It can present as a connective tissue dysfunction which mimics Ehlers-Danlos or Marfan's syndromes,² with joint hyperextensibility so severe as to lead to dislocation, high arched palate, and cutis hyperelastica. There may also be mild dysmorphic features such as epicanthic folds and large malformed auricles. Cardiovascular features include mitral valve prolapse and dilatation of the ascending aorta.³ We agree that fragile X is an important diagnosis to exclude, and accept the need to be selective in deciding which patients should be screened, but would suggest that the screening criteria might usefully be broadened to include patients with connective tissue or cardiovascular abnormalities with non-specific developmental delay. We also consider that full cardiological assessment should be performed in proved cases, because of the importance of diagnosing mitral valve prolapse and the need for appropriate prophylaxis against infective endocarditis in these patients.⁴

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1 Winter RM. Fragile X mental retardation. *Arch Dis Child* 1989;64:1223-4.

2 Hagerman RJ, Van Housen K, Smith ACM, McGavren L. Consideration of connective tissue dysfunction in the fragile X syndrome. *Am J Med Genet* 1984;17:1111-21.

3 Hagerman RJ. Mitral valve prolapse and aortic dilatation in the fragile X syndrome. *Am J Med Genet* 1984;17:123-31.

4 Lachman AS, Bramwell-Jones DM, Lakier JB, Pocock WA, Barlow JB. Infective endocarditis in the billowing mitral leaflet syndrome. *Br Heart J* 1975;37:326-30.

Fetal ascites: an unusual presentation of Niemann-Pick disease type C

SIR,—We read with interest the paper of Maconochie *et al* as we have recently seen a case of Niemann-Pick disease type C with an

almost identical presentation.¹ The baby was born to a 41 year old Pakistani woman, gravida 12 para 6. The parents were first cousins. The unfortunate obstetric history included four first trimester spontaneous abortions and a 29 week stillbirth. Another baby, an anencephalic, died in the neonatal period. Finally a girl, born at full term, died at 4 weeks of age after a three day illness characterised by fever, convulsions, and hepatosplenomegaly. Postmortem examination showed excessive deposition of sphingomyelin in the spleen.

In a subsequent pregnancy hydramnios was noted at 26 weeks' gestation. An ultrasound scan showed fetal ascites but no structural abnormalities. The baby was born at 34 weeks' gestation weighing 2590 g. There was gross ascites and hepatosplenomegaly. Jaundice was evident on the first day of life (total bilirubin concentration 111 $\mu\text{mol/l}$, conjugated bilirubin 83 $\mu\text{mol/l}$). During the next two weeks there was clinical and laboratory evidence of continuing hepatic dysfunction, and the baby died from liver failure at 19 days.

Investigations excluded other causes of fetal ascites and neonatal liver disease. Peripheral leucocyte enzyme assays were normal. Bone marrow aspirate showed foamy histiocytes. A percutaneous postmortem splenic histology specimen showed accumulation of sphingomyelin. Partial deficiency of sphingomyelinase was found in cultured skin fibroblasts. The fibroblasts showed appreciably reduced intracellular esterification of exogenous lipoprotein derived cholesterol, consistent with Niemann-Pick disease type C.

Clearly this disease should be considered in the differential diagnosis of fetal ascites and conjugated hyperbilirubinaemia in the neonate. Whether, in our case, any of the previous abortions or the stillbirth was affected is speculative. Undoubtedly, increasing experience with ultrasound will assist in antenatal recognition of the disease. With regard to postnatal investigation our case emphasises the importance of skin fibroblast culture. In addition to studying cholesterol esterification, partial deficiency of fibroblast sphingomyelinase may be found, whereas peripheral leucocyte levels are typically normal.

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1 Maconochie IK, Chong S, Mieli-Vergani G, Lake BD, Mowat AP. Fetal ascites: an unusual presentation of Niemann-Pick disease type C. *Arch Dis Child* 1989;64:1391-3.

The school health service through parents' eyes

SIR,—We read with interest the personal paper on the school health service by Dr Perkins and would like to make some comments.¹

It is important to have a clearly defined function communicated to all users of the service. At the moment many teachers misunderstand and have inappropriate expectations of what we should achieve, which leads to disappointment and downgrading of the service in teachers' eyes that is communicated to parents.

Inadequate facilities are provided in many schools, which must communicate lack of interest in the service to parents and children.

Difficulties arise because of rules that have developed for historical reasons—for example, we have little access to simple investigation and also most things must be referred back or through general practitioners before action can be taken. This apparent lack of authority even in areas of special interest must convey low status.

Certainly communication could be improved by having a named doctor and nurse visiting the school regularly throughout the school year. In order to do the job efficiently we must have a clearly defined role about which all users have appropriate expectations. We should be able to fulfil that role in as direct a way as possible to be seen as having appropriate authority. Above all it must be seen as a useful service to parents and teachers and children. These are the personal views of the signatories.

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1 Perkins ER. The school health service through parents' eyes. *Arch Dis Child* 1989;64:1088-91.

Chlamydia trachomatis in infants: a prospective study

SIR,—We were interested to read the paper by Preece *et al* dealing with chlamydial infection in children but feel that some important points may have been omitted.¹ In infants, *Chlamydia trachomatis* infects multiple sites including the rectum and vulva.² Screening from conjunctiva and pharynx alone may underestimate transmission from infected mothers. Where a more complete screening practice has been used, longer carrier status has been shown.³ Failure to recognise the reality of genital carriage, and especially the declaration that a child is free from infection on the basis of limited sampling, carries serious social and legal implications, as some practitioners regard the presence of vaginal chlamydia as an indicator of sexual abuse.⁴ Topical treatment of chlamydial conjunctivitis does not clear the child of the pathogen at other sites and leaves it vulnerable to completely avoidable respiratory infection.

Finally, we wish to challenge the assumption that antenatal screening for chlamydia is not cost effective. No account has been taken of an important part of the equation, namely the pregnant woman herself and of the morbidity she may avoid by receiving treatment earlier rather than later.

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1 Preece PM, Anderson JM, Thompson RG. Chlamydia trachomatis in infants: a prospective study. *Arch Dis Child* 1989;64:525-9.

2 Schacter J, Grossman M, Holt J, *et al*. Infection with *Chlamydia trachomatis*: involvement of multiple anatomic sites in neonates. *J Infect Dis* 1979;139:232-4.

3 Bell TA, Stamm WE, Kuo C-C, *et al*. Chronic Chlamydia trachomatis infections in infants. In: Oriol D, Ridgway G, Schacter J. *Chlamydial infections*. Cambridge: Cambridge University Press, 1986:305-8.

4 Ingram DL, White ST, Occhiuti AR, *et al*. Childhood vaginal infections: association of chlamydia trachomatis with sexual contact. *Pediatr Infect Dis* 1986;5:226-9.

Drs Preece, Anderson, and Thompson comment: Our recent paper explored the postnatal morbidity in infants associated with perinatal transmission of maternal *C trachomatis* infection. While it is interesting to document the persistence of rectal and vaginal carriage this was not our primary aim, and we agree that studies to document such carriage and persistence of infection are required to distinguish from later acquisition.

We agree that in clinical practice, oral erythromycin is now the treatment of choice in all chlamydial infections in children.¹

Finally, our statement about cost effectiveness of screening for maternal infection was based on the subsequent perinatal and postnatal morbidity in infants. The practicality and effectiveness of such a screening programme is discussed in more detail in our companion paper.² We feel that our data do not support such a programme to protect infants from chlamydial infection for the reasons outlined.

With reference to maternal infection, pregnancy may provide an opportunity to screen for *C trachomatis* infection in adult women. However, there may be other strategies that will be more logical and cost effective in the management of adult infection. As Drs Powell *et al* point out we do not address this issue, which needs more extensive and specifically designed studies of the epidemiology of *C trachomatis* infection in adult women.

1 Rettig PJ. Chlamydial infections in paediatrics: diagnostic and therapeutic considerations. *Pediatr Infect Dis* 1986;5:158-62.

2 Preece PM, Ades A, Thompson RG, Brooks JH. Chlamydia trachomatis infection in late pregnancy: a prospective study. *Paediatric and Perinatal Epidemiology* 1989;3:268-77.

Egg and breast milk based nitrogen sources compared

SIR,—In their paper comparing the effects of intravenous Vamin 9 glucose and Vaminolact on the plasma amino acid profile, Puntis *et al* discuss the possible neurotoxic effects of raised phenylalanine concentrations.¹ They conclude that Vaminolact is preferable to Vamin 9 glucose because it was associated with less marked increases in plasma phenylalanine concentrations. In support of this view they refer to findings in early treated children with phenylketonuria showing that intellectual outcome is inversely associated with average phenylalanine control during treatment (as well as age at the start of treatment).² I doubt whether it is appropriate to liken the effects of short term changes in phenylalanine in children receiving Vamin 9 glucose (which also caused rises in other amino acids including tyrosine) to the effects of longterm phenylalanine control in phenylketonuria, which is associated with decreased rather than increased concentrations of tyrosine.

It may be more useful to consider the likely effects of the raised phenylalanine concentrations on the uptake of amino acids into the brain.³ This will depend upon the plasma concentrations of the other large neutral amino

acids, as well as the phenylalanine concentrations and the transport characteristics of the blood-brain barrier. Although we know rather little about the latter in sick, human infants, comparison of the ratios of phenylalanine to the sum of the concentrations of tyrosine, tryptophan, and the branched chain amino acids in infants receiving breast feeds, Vamin 9 glucose, and Vaminolact provides a comparative measure of phenylalanine uptake in the three groups of infants.

Using the average plasma amino acid values in breast fed infants⁴ and in those given Vamin 9 glucose and Vaminolact¹ the ratios were 0.1, 0.35, and 0.27 respectively. The data suggest that phenylalanine uptakes into the brain in infants receiving Vamin 9 glucose and Vaminolact were similar, and that both products are likely to result in higher uptake of phenylalanine than breast feeding. In those infants receiving Vamin 9 glucose who had particularly high phenylalanine concentrations the ratio would be higher only if the concentrations of tyrosine and other amino acids failed to rise with phenylalanine. The increased ratio in infants receiving Vaminolact was largely accounted for by their lower tyrosine concentrations, and the ratios of tyrosine to the other large neutral amino acids (0.2, 0.2, and 0.06 respectively) suggest that tyrosine uptake was lower in infants receiving Vaminolact than in breast fed infants; in infants receiving Vamin 9 glucose it was similar. However, if tryptophan is considered the reverse situation pertains (ratios 0.13, 0.04, and 0.12 respectively).

These simplified ratios cannot be expected to give an accurate prediction of brain amino acid uptake but do provide useful comparisons. In the present state of knowledge it seems wisest in infants receiving intravenous amino acids to aim at plasma amino acid profiles similar to the averages observed in well nourished breast fed neonates. By this criterion Vaminolact requires the addition of tyrosine (and a reduction of threonine) before it can be said to be 'better' than Vamin 9 glucose.

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- 1 Puntis JWL, Ball PA, Preece MA, Green AS, Brown GA, Booth IW. Egg and breast milk based nitrogen sources compared. *Arch Dis Child* 1989;64:1472-7.
- 2 Smith I, Beasley M. Intelligence and behaviour in children with early treated phenylketonuria. A report from the MRC/DHSS Phenylketonuria Register. *European Journal of Clinical Nutrition* 1989;43:1-5.
- 3 Pardridge WM. Brain metabolism: a perspective from the blood brain barrier. *Physiol Rev* 1983; 63:1481-535.
- 4 Wu PYK, Edwards N, Storm MC. Plasma amino acid pattern in normal breast fed infants. *J Pediatr* 1986;109:347-9.

Drs Puntis, Ball, Preece, et al comment:

We thank Dr Smith both for her remarks on our paper and her interesting speculations. While we do not disagree with her comments, there are several points which should be raised in reply. We do feel that when examining available amino acid sources it is reasonable to focus attention on those amino acids such as phenylalanine that under certain circumstances are known to have deleterious clinical effects at high concentrations. Our data allow for certain generalisations to be made when comparing the two amino acid solutions, but we felt that Dr Smith is rather brave to make inferences about phenylalanine uptake by the brain in our patients. We did not conclude that Vaminolact is preferable to Vamin 9 glucose simply because it was associated with less marked increases in plasma phenylalanine, but because, in general, the plasma concentrations of the various amino acids (including phenylalanine and tyrosine) in Vaminolact fed infants tended to be closer to the mean described in breast fed infants than those in the Vamin 9 glucose fed group. By this criterion Vaminolact appears 'better' than Vamin 9 glucose. Whether or not we should be attempting to reproduce the amino acid profiles found in breast fed infants is a moot point and the ideal composition for amino acid sources remains a subject for debate.

Aneurysms of the vein of Galen

SIR,—We would like to add a small but

important point to the discussion of aneurysms of the vein of Galen by O'Donnabhain and Duff.¹ We would agree that surgery for the aneurysm itself is both difficult and seldom successful but may be a necessary part of the management of the infant with high output cardiac failure. Infants with hydrocephalus comprise a different clinical group who should undergo shunting as the initial surgical procedure. Having stabilised these patients with hydrocephalus it is important to be aware that further surgery may not be necessary as there are a number of cases in the literature in which the aneurysm has subsequently undergone spontaneous thrombosis.

All the reported cases of a thrombosed aneurysm of the vein of Galen presented initially with hydrocephalus, although one case presented with subarachnoid haemorrhage in addition to hydrocephalus. Spontaneous thrombosis does facilitate the successful surgical removal of the aneurysm, the first such case being a 5 month old boy described by Heinz *et al.*² Calcification of the aneurysm occurs in 14% of patients and the aneurysm may calcify completely. We have recently described a 3 month old boy with hydrocephalus whose aneurysm of the vein of Galen was completely thrombosed and calcified by 3 years.³ We now consider him 'cured' after ventriculoperitoneal shunting only and we would advocate that early surgery, if possible, be confined to the treatment of hydrocephalus.

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- 1 O'Donnabhain D, Duff DF. Aneurysms of the vein of Galen. *Arch Dis Child* 1989;64:1612-7.
- 2 Heinz ER, Schwartz JF, Sears RA. Thrombosis in the vein of Galen malformation. *Br J Radiol* 1968;41:424-8.
- 3 Chapman S, Hockley AD. Calcification of an aneurysm of the vein of Galen. *Pediatr Radiol* 1989;19:541-2.

SPRING BOOKS

Book reviews: some personal experience from the receiving end

Some years ago I wrote an invited annotation on book reviewing,¹ asking a question 'Who should be asked to review a book?' Should a general practitioner or nurse review a book by a consultant? Should a consultant review a book by a general practitioner or nurse? I was unable to answer my own questions.

There is a striking dearth of articles on reviewing books—and there have been only a few on an allied subject, the refereeing of papers. An excellent article on book reviews was that of the late Dr Irving Wolman, when editor of *Clinical Pediatrics*.²

An author's ego may be boosted (perhaps undesirably) by a laudatory review, or punctured by a derogatory one. The author is helped by positive criticisms, which can be attended to in a further edition, but is not helped by vague expressions of distaste for a book with no specific criticisms, which enable the author to form his own conclusions as to the extent of the reviewer's knowledge, the thoroughness or otherwise with which he has read the book, or its reviewer's personality. It is annoying to be criticised, as I often have, for statements that one has never made and would not dream of making. A reviewer of my book *Common Symptoms of Disease in Children* clearly thought that the title of my book was 'Symptoms of Common Diseases in Children' and attacked it accordingly. A British journal, publishing a review of one of my books, even misspelt my name; and two other British journals got the title of my book wrong.

Over the years I have amassed experience of many different reviews of my books, and I felt that some of this experience would be of interest to others—and raise the question of who should be asked to review a book.

Many reviewers pick out three or four of what they consider to be glaring, important, or typical faults. Below are some examples from reviews of my books—recorded without comment—knowing that readers may or may not agree with the criticisms. I was criticised for giving the following advice or opinions:

(1) (In the days of smallpox vaccination) that mothers should not be vaccinated in pregnancy.

(2) (In a book for non-medical readers) that for certain (named) countries abroad, children should be immunised against cholera, even though it is not 100% effective.

(3) that children should be immunised against tetanus (along with diphtheria and pertussis).

(4) that the word 'measles' was derived from a Latin word meaning 'miserable'.

(5) that ear pain due to acute otitis media should lead to prompt antibiotic treatment.

(6) (After a discussion on indications for circumcision) that the decision as to operation should depend only on the interests of the child, and not on the wishes of the parents.

(7) that a diabetic child should always carry a lump of sugar or sweets in case of hypoglycaemic symptoms. The reviewer disagreed, saying that the child should always carry glucagon.

(8) (After a 12 page discussion on the difficulties of diagnosing the cause of acute abdominal pain in children) I said that 'it follows that there should be no hesitation in calling in expert advice when one is faced with the problem of a child with acute abdominal pain'.

(9) that a child with a significant delay in speech development should be assessed by an expert.

(10) that 'it is worthwhile to refer the clumsy child to an expert, for the diagnosis can be difficult'.

(11) that a deep congenital dermal sinus, persisting to the age of 2, should be referred to a surgeon because of the risk of infection.

(12) that postnatal discharge in, or after, a cold, may make a toddler cough when he lies down at night (on his back).

A reviewer wrote that the milestones of development given by me (largely based on the quoted work of Arnold Gesell, Albrecht Peiper, TB Brazelton, French workers, and numerous other experts) were wrong, and should be altered.

Reviewers drew attention to my faults of omission, on the grounds that:

(1) In a discussion on the treatment of nappy rashes, I should have recommended the sprinkling of boric acid crystals into the nappy.

(2) In a chapter on variations in babies' development, I failed to draw the line between normal and abnormal.

(3) In my book for school teachers, I failed to devote a section to the Spitz-Holter valve.

(4) In a discussion of teething, I should have written that the mother should be advised to give extra fluids.

(5) In a discussion on insufficiency of breast milk, I should have written that it should be managed by telling the mother to increase her energy intake.

These reviewers' criticisms draw attention to the difficult task facing the editors of journals in choosing someone to review books—and even in deciding whether the reviews should be published. Should book reviews be checked by referees—and how would the referees be chosen? I have no answer to the editors' problems.

R S ILLINGWORTH

1 Illingworth RS. Some reflections on book reviews. *J R Soc Med* 1977;70:119-21.

2 Wolman I. What makes a good medical book review? *Clin Pediatr (Phila)* 1962;1:29-32.

ABC of Clinical Genetics. By Helen M Kingston. (Pp 62; £10.95 paperback.) British Medical Association, 1989. ISBN 0-7279-0263-6.

Many readers of the *Archives* will already be aware of this series of articles from the *British Medical Journal*. They have now been published together in a slim volume, which guides the reader from mendelian to molecular genetics and beyond, outlining the principles involved and showing how these relate to clinical practice.

In the first chapter Helen Kingston summarises the organisation of clinical genetics services. The need for liaison between geneticists and other professionals in hospitals and community is emphasised. Optimal management of genetic disease, for patients and their families, involves integration of many disparate skills and until those providing these skills can speak one language the geneticists' task will remain a difficult one. In the succeeding chapters many of the more commonly encountered genetic conditions are used to illustrate the approach of the clinical geneticist to chromosomal, single gene, and polygenic disease.

Several chapters deal with areas where

common investigative approaches naturally link groups of conditions. One on genetics and cancer illustrates the ways in which DNA investigation both aids management of familial cancers and is shedding light on tumour aetiology and evolution. Another suggests a framework for approaching the patient with dysmorphogenesis. The importance of appropriate investigation of the malformed fetus and stillborn child is emphasised. A further chapter describes techniques used in prenatal diagnosis. Ethical issues are mentioned, but only briefly and perhaps warranted a chapter themselves.

The final chapters focus on molecular genetics and its application to clinical medicine. The techniques that have enabled recent and rapid progress at the scientific-clinical interface are summarised. The fact that some of the information on these pages is already out of date highlights the rate of this progress and the need for all clinicians to have access to a geneticist working at this interface.

This little book is worthy of a few hours of any health care worker's time and it will be widely read. The appendix includes addresses of many of the lay support organisations involved with specific genetic diseases. Those who familiarise themselves with the preceding pages will also be in a position to know what

help they can expect from their regional genetics service.

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Textbook of Pediatric Dermatology. Edited by Ramon Ruiz-Maldonado, Lawrence Charles Parish, J Martin Beare. (Pp 863; £114.00, hardback.) Grune and Stratton (Harcourt Brace Jovanovich), 1989. ISBN 0-8089-1863-X.

I finished my paediatric clinic, drove home, and opened the parcel to reveal a large cream new *Textbook of Pediatric Dermatology*. I perused the index for lichen sclerosis et atrophicus having just told doctors at the clinic to avoid misdiagnosing the condition as sexual abuse. However, to my disappointment, it was not mentioned and under the heading sexual abuse, only sexually transmitted diseases were considered. I then opened the book at the beginning and things began to improve.

This is a well produced book with 70 chapters contributed by 80 authors from many countries. One problem for editors with so many and scattered authors is getting all manuscripts returned quickly and failure to achieve this results in delay in production of the book and the danger of a dated content. However, I did

find the book to be well referenced with references up to 1988 appearing in many chapters.

Most topics in paediatric dermatology are considered, and these include genodermatoses, blistering disorders, infections and infestations, tumours, hair and nails, atopic dermatitis, psoriasis, and cutaneous manifestations of paediatric disease.

Some minor criticisms. I would have expected more on neonatal cold injury, mention of actinic prurigo, hydroa vacciniforme, and tetracycline staining of teeth. Who still uses resorcinol in acne? The importance of clinical differentiation of the benign Buschke-Ollen-dorff syndrome from pseudoxanthoma elasticum should have been emphasised and recent work by Pope *et al* on Ehlers-Danlos syndrome type IV merited mention. I would not agree that Crohn's disease is rare in adolescence or that involvement of the dorsum of the toes is a characteristic of juvenile plantar dermatosis. The editors could have been more thorough at reducing some repetition of the same disorders by different authors.

The index is good and comprehensive and I found no spelling errors in it. Illustrations are all monochrome and a minority which have reproduced poorly should have been omitted. I assume that colour illustrations would have resulted in a more prohibitive cost.

In 1988 a larger two volume *Pediatric Dermatology* text appeared (Schachner and Hansen) which has been well received. I think this one volume tome at half the cost bears favourable comparison.

I recommend that dermatology and paediatric departments purchase this very readable reference book. Unfortunately the price is too high for many individual doctors to buy a copy for themselves.

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Dewhurst's Practical Paediatric and Adolescent Gynaecology. Second Edition. By D Keith Edmonds. (Pp 148; £40.00, hardback.) Butterworth Scientific Limited, 1989. ISBN 0-407-01520-5.

Sir John Dewhurst established a unique understanding and experience in the very specialised field of paediatric and adolescent gynaecology which is nationally and internationally renowned. This is acknowledged in the altered title of this second edition of his classic book, which has been revised and updated by his 'apprentice' Keith Edmonds.

The adjective 'practical' is justifiably chosen, and the book provides a complete catalogue of detailed and thorough advice on the clinical features, aetiology, investigation, and treatment of all gynaecological problems of childhood, from ambiguous genitalia at birth to pregnancies in adolescents. Each chapter includes a careful list of references to relevant detailed studies and reviews.

This book provides an essential reference work for first line management of what are such important and yet uncommon conditions in the experience of most gynaecologists, and where erroneous initial treatment can have such unfortunate long term results. The advice on appropriate emotional care and understanding of the young patient and her parents is particularly helpful.

The book is written from the gynaecological point of view and essentially concentrates on the gynaecological aspects of these problems. Nevertheless it must be essential reading for paediatricians, and an important reference work for general practitioners.

The one disappointment is the surprisingly brief treatment of the problems of suspected or actual child sexual abuse. The author describes the conditions of vaginal discharge and vulvitis as being 'probably the only gynaecological disorders of childhood which may be thought of as common', but those of sexual abuse are becoming almost equally so (although the referral pattern may well be, rightly or wrongly, biased by the gender of the doctor!).

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Yearbook of Pediatrics 1989. By Oski Stockman. (Pp 683; £40.00, hardback.) Wolfe Medical Publications Ltd, 1989. ISBN 0-8151-6561-7.

Another year must have passed. I'm a year older (a bad thing) and another edition of the Yearbook has arrived (a good thing). We have both put on weight. The Yearbook has expanded from 550 to 670 pages and I've (well that's a secret).

It's hard to say anything new about the Yearbook, which is an old friend, and this edition maintains the high standard of previous years. The whole range of paediatrics is covered by original articles, and most are followed by fairly long editorial comment, always erudite and humane, and often funny. The usual helpful list of review articles is included.

How could the Yearbook be improved? Some years ago the American Academy of Pediatrics published a review of the Doman-Delacato programme, and pointed out that there was no objective evidence at all that this very expensive and arduous treatment benefited handicapped children. I wonder if the editors would consider commissioning occasional similar special articles on controversial subjects which would then have the authority of the Yearbook behind them? Subjects that could be considered include subclinical copper deficiency as a cause of fractures, hair analysis as a diagnostic test, the role of oxygen in the retinopathy of prematurity, and so on.

I do have one criticism. Very few papers from outside the United States are mentioned. Of 49 papers on oncology, haematology, and urinary tract, 36 are from America and none from the United Kingdom. Is no research carried out in this country, or should the editors widen their horizon?

The Yearbook is essential reading for any paediatricians who want to keep up to date, and I strongly recommend it.

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Consultant paediatrician

Molecular Medicine: Cystic Fibrosis. By Peter Goodfellow. (Pp 96; £15 paperback.) Oxford University Press, 1989. ISBN 0-19-261835-0.

When I was invited to review this book I seriously considered declining as molecular medicine is not one of the strings of my bow. However, I thought, as this was the case at least if I read the book I might learn something. Few clinicians who have left medical school for longer than 10 years have more than a basic understanding of cellular chemistry let alone molecular biology. Most paediatricians, however, have some understanding of the clinical disorder of cystic fibrosis. One of the purposes of this review was to discover if this book would enlighten we clinicians who are so sadly ignorant about the basic sciences on the recent advances in the understanding of the

cellular defects in subjects with cystic fibrosis and the identification and location of the cystic fibrosis gene.

There are five chapters. Three cover the natural history, management, and prenatal diagnosis of cystic fibrosis and present a well written synopsis of the subject, accessible not only to non-medical research workers but also to lay readers. The other two describe the defects in epithelial ion transport and molecular genetics of cystic fibrosis. For the average clinician these chapters are undoubtedly difficult. However, those working in the subject at the interface of clinical and laboratory science will find them comprehensive, up to date and well referenced. It is for this latter group that I think this book will be most useful.

Sir Peter Medawar, in answer to criticism that too much scientific specialisation meant that scientists could no longer communicate with each other, said that 'scientists are getting less specialised not more'—physicists and chemists have entered the world of biology—and 'the reason [they] seem so seldom to communicate with each other is that they do not really want to . . . they want above all to be left to cultivate their gardens'. Certainly this book illustrates very well how the varied contributions of chemists, molecular biologists, clinical scientists, and others make for the understanding of 'that shapely whole' and while each may not understand how the other cultivates his garden at least we may all obtain a concept of how growth is proceeding.

S MCKENZIE
Consultant paediatrician

Handbook of Neurological Investigations in Children. By John B P Stephenson and Mary D King. (Pp 244; £25 paperback.) Butterworth Scientific Ltd, 1989. ISBN 0-7236-1295-1.

What a welcome book to the slightly dull world of paediatric neurology. The authors have tackled their subject with enthusiasm and have produced a very readable and thought provoking book. The very individual approach adopted towards investigation of children with neurological disorders has made the subject very tangible for general paediatricians.

The first section of the book is devoted to each individual test and every chapter ends with well illustrated case histories. A step wise approach to investigation is supported and shopping lists are definitely out! The philosophy of investigations, their benefits, and harmful effects are discussed sensibly. We are provided with an up to date account of the most appropriate investigations available in the late 1980s. The chapters on electroencephalography and diagnostic imaging are particularly good. Although the chapter on biochemistry looks daunting, it is very readable and gives a succinct account of the variety of tests available. The linking of biochemical tests to clinical information enables easier digestion of the information.

The second half of the book is devoted to a problem orientated approach to investigation. This works very well and compliments the first half of the book well. The authors cover a wide range of common topics—some rather too briefly.

Each chapter is well referenced and the 10 page index is comprehensive.

This book is essential reading for all paediatricians, especially those in training, and the odd paediatric neurologist might consult it. These authors are a successful team

and I hope that we see them collaborating in the future!

Health warning—this book could seriously affect your future approach to paediatric neurological investigation and hopefully for the better.

B M MACARDLE
Consultant paediatrician

The Hereditary Hemolytic Anemias. Edited by William C Mentzer, Gail M Wagner. (Pp 476; £52.50, hardback.) Churchill Livingstone, 1989. ISBN 0-443-08242-1.

When the nineteenth century investigators first squinted down the microscope at blood cells and identified diseases they had no idea of the explosion of knowledge that would follow. A blood specimen is so easily obtained that the red cells have been studied in enormous detail, and a vast amount is known about their diseases, some of great rarity. Professor Mentzer is a paediatric haematologist and Dr Wagner is an adult haematologist. Their book is a comprehensive review by a selection of authors from the San Francisco Bay area of the hereditary red cell disorders which lead to haemolysis. After an introductory chapter by the editors, there are chapters on diagnostic strategy, and subsequent chapters on the thalassaemia syndromes, sickle cell disorders and unstable haemoglobins, membrane disorders, metabolic disorders, haemolytic disease of the newborn, mechanisms of red cell destruction, and a final chapter, which is the shortest in the book, on treatment.

The book is not written specifically for paediatricians. It is strong on pathophysiology and weak on management. The chapter on haemolytic disease of the newborn is an exception, so although the subject is not really hereditary, it is well worth reading. The other chapters are useful for reference. The need to be comprehensive means that a page and a half of table is given to classifying the 29 variants of glucose phosphate isomerase associated with haemolytic anaemia. Fortunately the editors have resisted the temptation to include the 150 variants of glucose-6-phosphate dehydrogenase. This is a problem with the haemolytic anaemias: all this information has to be recorded, but its relevance to the day to day management of the haemolytic anaemias that make up the day to day business of a paediatric clinic is slender in the extreme. Nevertheless, this is a good book for looking up the rare disease, for help with an unusual problem, and for throwing light on the dark mystery of the unsolved cases of haemolytic anaemia which puzzle every haematology department.

D I K EVANS
Consultant haematologist

Paediatric Clinical Examination. By Denis Gill, Niall O'Brien (Pp 188; paperback.) Churchill Livingstone, 1988. ISBN 0-433-03956-9.

'Learn to see things' is one of many quotes included in this book, and it is sound advice by Leonardo de Vinci, applicable to the field of paediatrics as well as to art. It can be remarkably difficult to 'learn to see things' in children without adequate guidance and practice, and yet little has been written on the subject. Denis Gill and Niall O'Brien aimed to fill this gap with an entertaining, concise and

readable handbook that provides a simple approach to clinical examination of children.

The book is aimed at undergraduate medical students taking their paediatric course and also at postgraduate doctors commencing their first post in paediatrics. It provides a simple and thoughtful approach to history taking and examination at different ages, particularly in the newborn, infant, and preschool child. The text is written in a very humorous way which makes it easy to read as well as instructive. The authors' prime objective is to put the principles into practice by examining as many children as possible. If they fail to do this in some cases, I think it suggests that the student would be better suited to another specialty, rather than reflecting badly on the text.

In conclusion, I think that this book fills an important gap in the literature, and that students in paediatrics will find it an invaluable guide to the art of approaching children.

C SMITH
Senior registrar in paediatrics

Linear Growth Retardation in Less Developed Countries. Edited by J C Waterlow. Nestle Nutrition Workshop Series, Vol 14. (Pp 295; \$50 hardback.) Raven Press, 1988. ISBN 0-88167-378-1.

This book contains a wealth of interesting information about human growth and nutrition. Unfortunately it cannot give a definite answer to the key question 'Is stunting accompanied by biological functional impairment?'

The size of the problem is not in doubt; 39% of preschool children in developing countries are stunted, less than -2 standard deviations below the most widely used reference figure for height for age (National Center for Health Statistics). This compares with only 12% who are wasted, with a weight for height less than -2 standard deviations (Kellar, chapter 2). The importance of stunting is less clear. Studies from Zaire (Van Lerberghe, chapter 14) do not confirm earlier findings from Bangladesh that there is an increased risk of death in children who are stunted. Most authorities accept that stunting has a definite association with poverty, poor living standards, and incomplete recuperation in adverse environments. Waterlow declares that 'both physiological and political aspects of stunting are important', but Tanner, the high priest of auxology, considers that 'height is only important as a proxy for social deprivation between groups'.

All who are interested in child growth should read this book, and no paediatrician can deny a concern about a process so fundamental to our specialty. Here are a few points, not all related to linear growth, to whet the appetite. Many are not new but some are based on recent research.

In malnutrition the growth related hormonal systems that are most affected are those of growth hormone - somatomedin (Rappaport, chapter 7). After malnutrition there is little catch up in height until there has been an increase in weight so that the weight for height ratio exceeds 85% of the reference values (Golden, chapter 9 and Nabarro, chapter 10). Zinc deficiency does cause decreased linear growth and supplementation increases growth rates in stunted male but not stunted female infants (Golden, chapter 9). Zinc increases the metabolic efficiency of dietary energy utilisation (Tomkins, discussion after chapter 9).

Growth is very seasonal in Nepal, stunting is maximal in August to November but the peak weight gain occurs within the same period, mid August to mid October, followed by the peak height gains from mid December to mid April. Children between 12 and 24 months of age grow 1.5-2 cm in three months, but show no growth in height the rest of the year (Nabarro, chapter 10). There is no causal link between stunting and developmental delay or impaired intellect, both are associated with the effects of poverty and deprivation. Mental development is highly dependent on biological and environmental influences in the first two years of life. There is evidence that early stimulation can to some extent compensate for the negative effects of early malnutrition. 'The family environment... is a fundamental determinant' (Colombe, chapter 12). Physical work capacity, as measured by maximal oxygen consumption, is largely dependent on muscle mass which correlates with nutritional state. There are implications that undernourished children will become adults with a reduced physical work capacity (Spurr, chapter 13).

In the final chapter on the significance and implications of the findings of the symposium for health policy, Gopalan introduces some interesting unpublished data from India about the associations between birth weight, nutritional state, and family income. He also makes a few inaccurate over simplifications, 'stunting is... invariably associated with poverty'. However, in the context of a scientific meeting supported by the largest infant food multinational corporation he speaks out courageously about the abuses of commercial baby foods by the urban poor. He has data to show that 22-30% of the poorest mothers in Indian cities are using commercial milk substitutes with 'results that can only be described as disastrous'.

W A M CUTTING
Senior lecturer

The Baby Under 1000 g. Edited by David Harvey, Richard W I Cooke, Gillian A Levitt. (Pp 353; £65 hardback.) Butterworth Scientific Ltd, 1989. ISBN 0-7236-0952-7.

This book concerns the management of babies under 1000 g. It has been rather extravagantly claimed (not in this book) that a full term baby has more in common with a teenager than with a baby of 24 weeks' gestation. Certainly very preterm babies are different. Hence this book.

Some aspects of management are not that different, however, and despite valiant efforts by the contributors some chapters read much the same as they would have done had the title of the book been 'The Ill Baby under 2000 g'. Some such chapters, for example the one on ventilator care, are nevertheless very enjoyable. The authors of the chapters on the skin, calcium and phosphorus metabolism, and renal function have an easier time of it. Other stimulating chapters include those on monitoring and neurological abnormalities.

The 32 contributors to this book between them work in 18 different centres—all but three of which are in the United Kingdom. As well as 17 chapters on different aspects of the medical care of the baby under 1000 g there are eight chapters on the subjects of epidemiology, obstetric management, nursing care, emotional needs of the family, cost of care, and outcome. Most subjects are covered clearly and practically with remarkably little repetition. A lot of references are cited.

I would have liked more discussion of the

relative roles of pulse oximetry and skin electrodes in monitoring oxygenation both with and without an indwelling arterial catheter. There are too many abbreviations; 77 are listed in the glossary.

The publishers claim it is the first book to deal specifically with the baby under 1000 g. This book would be enjoyed by any paediatrician who looks after very preterm babies.

B W LLOYD
Consultant paediatrician

Celebration. By Margaret Spufford. (Pp 121: £2.95 paperback.) Collins, 1989. ISBN 0-00-627449-8.

This is a remarkable book. Written by the mother, it describes the discovery and progress of the daughter's cystinosis and the mother's own agonisingly painful idiopathic osteoporosis. It shows the need despite these afflictions to provide as loving and as normal a family environment both for the son's childhood and one in which, despite the family's extra tribulations, the father could function and work as the breadwinner. It is written with the impartial clarity of her profession as an academic historian. Even when describing severe stress and extreme suffering there are discerning and important observations about the medical world including occasions when despite the most stressful circumstances, the family could see with wry humour the absurdity of the predicaments in which they found themselves.

While the doctors sought to establish the diagnosis of cystinosis in her daughter by a series of invasive tests 'now I discovered, as I held a baby who was increasingly only capable of screaming "Mummy" that my instinct to defend her threatened to override my instinct to protect her in the long term, and therefore to get a diagnosis'. 'We were long past wanting her to live at any cost for possessive reasons, because we had so much wanted this child. What was intolerable was watching her learn fear'. 'She learned fast. I am never going to be able to forget the sound of her screams'.

It is of the greatest importance at this time when reorganisation of the NHS is being considered to listen to Dr Margaret Spufford when she says 'I have come seriously to doubt whether life should be sustained when it can only be done through massive and repeated medical intervention, especially when there is no community care, apart from the family, to which these young adults can suitably move on'. It is a message of the greatest medical and social significance that this girl, who on three occasions had been prevented from dying by major medical procedures, had in her adolescence become friendless, and acutely lonely. Sadly the parents realised that while they had been able to help a baby and a small child that they were much less able to help a girl of 18. They realised that she had lost her peer group as a result of the innate effects of the disease and of too much isolating medical experience. 'By definition she needed such a group above all things. As parents we had become less resilient to conquer the next obstacle in our fifties than in our early thirties. We had learned by now that there always is a next obstacle'.

Why then call her experiences 'Celebration'? In this short review it is not possible to describe the difficult pathway by which Dr Margaret Spufford reached the stage when she could see that the family's experiences con-

tained genuine achievement and reason for celebration as well as so much pain and suffering.

While this book describes how one individual family won through and how her religious faith was crucial to the mother's personal contribution, there is help here for people of many different beliefs as well as practical advice for both those needing care and those who provide it whether they are religious or non-religious. This is an important book for all those involved with medical ethics as well as those concerned with the future of our health services both inside and outside hospitals.

F BRIMBLECOMBE
Honorary professor of child health

Health. By the children of Walsall.

This little booklet was written by children of varying ethnic origins who attend a school in Walsall. It deals with their reports of their illnesses and accidents: it reveals their attitudes, priorities, and imagination.

The first priority would appear to be 'How many days off school for this'—they can tell you almost to the day!

Heroism—its here. 'I fell down my grandad's stairs—a four inch nail went through my head. Nobody knew for three weeks'. You'd have thought they would have noticed when combing her hair!

Misfortune—'When I was two, I was crying because I had fallen over. My mother took me upstairs to cheer me up. After a while I fell downstairs'. Shades of Gerard Hoffnung!

Attention to detail—'Over in America I had an accident in a car, I went in the car and I put my gear on and the car started to move. It hit a restaurant'.

Frustration—'When I was born, I turned blue. For two weeks I was stuck in an incubator with half a plant pot on my head'. The seeds of an idea?

Children as therapists: tummy upset—'Drink brandy and wine and go to the toilet' (seems like a good idea!) and warts—'Rub some bacon on it'. Lumps—'If I had lumps, I will go to the doctor and get some medicine and lie down. In two days I will feel better'. Such precision. Something in my eye—'I would tell my brother to blow it'. Why? What had he done wrong? Cannot sleep—'I imagine a sheep and I say this sheep is green, it is 11 years old it is 7 stones and its name is Samantha and I just close my eyes when I'm saying it'.

We should all read this booklet. It is refreshing, joyful, and unstuffy. It reaffirmed my decision to look after children.

G MCCLURE
Consultant paediatrician

Paediatric Hepatology. By Stuart Tanner. (Current Reviews in Paediatrics.) (Pp 363; £29.50 hardback.) Churchill Livingstone, 1989. ISBN 0-443-03393-5.

This latest edition in the series of *Current Reviews in Paediatrics* published by Churchill Livingstone aims, along with the preceding editions, to provide an overview of a current topic relevant to acute care paediatrics. These books are published by single authors and represent the experience of someone at the forefront of the field. In this sense Dr Stuart Tanner is a more than suitable choice for this particular edition.

The book starts with a description of the assessment of liver function, including both physical examination and history taking, and the current developments in biochemical investigation and imaging. The chapter is a well drawn out introduction to the topic and contains many of the latest advances that are currently available. The succeeding chapters are of particular relevance to neonatologists in the dealing of both cholestatic jaundice and hepatitis in the neonate and infant. These are set out in an extremely practical way and furnished with a lot of useful, up to date references and quick and easy to follow tables. The section on hepatitis has at last made clear to me the complexities of antigen and antibody rises and falls and their aid in the diagnosis of, particularly, hepatitis B infections and have certainly cleared up several of the problems surrounding hepatitis B screening in the antenatal population.

The latter part of the book deals successfully with metabolic diseases, more specifically Reye's syndrome, and the role of trace elements within the liver. In this section Dr Tanner has done an excellent job in calming the fears of the non-biochemists among us in providing a suitable and easily readable account of some of the more complex disorders of enzyme deficiencies within hepatology and I certainly found this section very helpful.

After the discussion of topics including cystic fibrosis, liver failure and cirrhosis, the book ends with a chapter on the current state of play in liver transplantation. This is an extremely important chapter with the current focus of media attention upon liver transplantation in young children and, in my opinion, almost justifies the reading of the book. The latest figures are presented in an easily accessible way and both the complications and indications for liver transplantation are well set out.

In conclusion, Dr Stuart Tanner, in producing the latest addition to this series has kept up the excellent tradition maintained by his predecessors. The book is moderately priced and as such should be available in most general paediatric departments and is certainly well worth reading for those people about to embark on the Membership examination.

N MEADOWS
Consultant paediatrician

Surfactant Replacement Therapy. Edited by Donald L Shapiro, Robert H Notter. (Pp 321: \$69.50 hardback.) Alan R Liss, 1989, ISBN 0-8451-4281-X.

In the past few years a deluge of knowledge of surfactant has opened on the unwary, jobbing paediatrician. The effect has been to excite, confuse, and alarm but, most importantly, to expose our ignorance. This volume of over 300 pages sets out to rectify this last problem while maintaining our excitement; these aims have happily been achieved.

The volume consists of two sections dealing with the fundamentals of lung surfactant and the clinical aspects of surfactant replacement therapy. The first is probably of more interest to the clinician as this is the area with which we are less familiar. Some little part will be above the heads of most of us but most is written lucidly and, whereas the subject is complicated, the reader will finish with a profound knowledge of the complexity of the subject.

The volume begins with an overview of surfactant, the historical background, and takes us forward to the concept of gene cloning. There follows a treatise on the physical chemistry and physiological activity of pulmonary surfactants and this chapter is succeeded by one on surfactant proteins, those mysterious molecules that are, at once, fundamental to the function of surfactants while being unwilling to yield their secrets.

The chapter on surfactant and lung liquid absorption at birth is revealing, at least to the reviewer, but one wonders if the only function of fetal lung liquid is 'a template for fetal lung growth'.

Alan Jobe takes us through the metabolism of lung surfactants explaining what is known, nudging us towards the unknown, raising questions along this way. One example—it would appear that exogenous surfactant does not impair endogenous surfactant synthesis but isn't this odd in a biofeedback system?

The chapter on immune complexes formed in response to surfactant administration is disturbing. Whereas no clinical effects of such complexes has been described, they may pose problems in the longer term.

The chapter by Bengt Robertson on microscopy both without and with surfactant replacement lends weight to the argument that such treatment improves lung function. Again, he raises problems of lung poor size and protein fluxes which will stir the reader from any intellectual lethargy.

The second half of the book deals with the variety of surfactants so far used in clinical trials. Much of the work has already been published so the reader is able to relax more into this section. Again, the authors are at pains not to be too hopeful, to draw attention to some potential disadvantages.

Altogether, I found this book stimulating and well worth reading. My major criticism is that, overall, it may be a little too enthusiastic. I doubt whether surfactant will prove to be a panacea and would have liked to see a discussion of surfactant failures. My other criticism is that, yet again, little is mentioned of European work—an all too common complaint of American books.

G MCCLURE
Consultant paediatrician

Paediatric Secrets. Edited by Richard A Polin, Mark F Ditmar. (Pp 447; £35.95 paperback.) Hanley and Belfus, 1989 (C V Mosby). ISBN 0-932883-14-1.

As medical literature continues to emerge at an overwhelming rate, it is refreshing to find a new book which is original, well presented, and a pleasure to use. The concept is simple: those questions commonly asked by American paediatric residents have been collected and then answered by a group of paediatricians associated with the Children's Hospital of Philadelphia. The areas covered include pathophysiology, clinical management, diagnostic tricks, specific diseases and definitions, useful physiological data, and a few delightful oddities (Ondine's curse is compared with 'intern's curse', mortals who are affected by not sleeping when they breathe!).

The title is misleading and does not do justice to the contents. Although it may be aimed at the resident (or senior house officer) who needs to have all the answers during a ward round, it has a much wider potential use. Candidates for the MRCP examination will use it for gathering information and paediatricians

will find it valuable for teaching sessions, *viva voce* examinations, and for clinical management information. Each major system has a separate chapter, and each question is followed by succinct, up to date information or advice. The information is presented as a discussion, or in lists and tables. There are a few line drawings and useful flow diagrams.

There is an inevitable American bias, and although some treatment advice is less useful in the UK (for example, the management of acute asthma or immunisation schedules) most information presented is pertinent and valuable. Some areas are particularly well covered, for example the treatment for necrotising enterocolitis and the discussion of Kawasaki disease are very good. It was wonderful to find precise information that is sometimes difficult to track down elsewhere.

There are a few errors and inconsistencies but the scope and accurate detail of the areas covered are remarkably comprehensive.

This is a fascinating, useful book and I would urge all paediatric departments to have a copy. Junior paediatricians can use it to outwit their seniors, or examiners and consultants can dip into it at leisure, remind themselves of the answers to 1819 questions, or use it as a valuable reference for clinical problems.

J STROOBANT
Consultant paediatrician

The Parents' Directory. Compiled by Fiona McDonald. (Pp 260; £5.95 paperback.) Bedford Square Press, 1989. ISBN 0-7199-1235-0.

Eight hundred voluntary organisations are listed in this helpful directory for parents. The variety of potential help is enormous. There are five main categories dealing with education, family welfare, handicap, health, and leisure. Finding one's way around this directory is slightly irksome. The rather incomplete index does mean that the reader has to wade through several categories before finding certain entries. One could quibble about some listings in the health and handicap categories. Despite these shortcomings, this book does provide a useful reference source for parents. Any professionals working with children should have access to a copy.

B M MACARDLE
Consultant paediatrician (community child health)

The Fragile X Syndrome. Edited by Kay E Davies. (Pp 135; £15.00 paperback.) Oxford University Press, 1989. ISBN 0-19-261836-9.

This book draws together in a compact work the increasing volume of information on this the second commonest cause of mental retardation after Down's syndrome. The fragile X syndrome, recognisable cytogenetically under certain conditions by a gap (fragile site) at Xq27 on the X chromosome, is unusual among X linked disorders in that as many as one third of obligate carrier females are mentally retarded. Even more fascinating is the fact that the condition may be transmitted through clinically and cytogenetically normal males.

Five authors, distinguished in their respective fields, cover the important aspects of the clinical manifestations, epidemiology, behaviour and treatment, and DNA and cytogenetic studies.

Paediatricians and clinical geneticists alike will find Jean-Pierre Fryns' clinical descrip-

tions and accompanying photographs useful; the classical clinical triad of moderate mental retardation, long face with large everted ears and macro-orchidism often seen in the post-pubertal fragile X male is less evident in the prepubertal male in whom relative macrocephaly is more striking and macro-orchidism is uncommon. Randi Hagerman emphasises the important correlation of the fragile X syndrome with autism and describes the characteristic behavioural patterns of affected individuals, which not only provide important clues for the diagnosis but also allow appropriate treatment and educational programmes to be devised. Useful comments are included on seeking and treating associated problems, such as pes planus, strabismus, hernia, scoliosis and mitral valve prolapse, which is said to affect as many as 50% of males. Treatment with folic acid is perhaps a more controversial issue than the author suggests.

The syndrome occurs in all ethnic groups and Tessa Webb's chapter on epidemiology emphasises the need to define the populations for which prevalence figures are being derived.

At the molecular level, a number of theories have been proposed by various authors to explain the basis of this unique disorder; these are lucidly summarised by Ted Brown. The gene itself is proving to be elusive and it has been difficult to identify DNA markers which are consistently close to the fragile X locus. Ted Brown describes, however, how in some families, use of flanking DNA markers may help in carrier detection studies.

Neils Tommerup highlights the cytogenetic 'catch 22'; males and females with non-specific mental retardation ideally should be tested cytogenetically for the fragile X marker but this adds a heavy workload to the laboratories, as many cells need to be screened (only a proportion express the fragile X marker) and special culture conditions must be met.

One minor criticism is that most of the authors refer to the 'female heterozygote' without defining whether this refers to obligate carriers on pedigree grounds or those who manifest the fragile X marker, or both. One small point of omission is that no specific mention is made of the fact that, unlike in other X linked disorders, most mothers of a boy with fragile X are thought to be carriers.

This book will be of great value in promoting awareness and understanding of this important disorder among paediatricians, who may well wish to purchase their own copy. The genetic idiosyncrasies of the disorder (for example, only 50% of obligate carrier females express the fragile X marker) highlight the need for referral to a clinical geneticist for carrier detection studies in females (and males) at risk, and for prenatal diagnosis counselling. Clinical geneticists themselves will find the book useful; Neils Tommerup's check list for prenatal diagnosis being an example. Cytogeneticists and molecular geneticists will also find a helpful 'state of the art' summary of the fragile X syndrome.

E M THOMPSON
Consultant clinical geneticist

Sudden Infant Death Syndrome. Edited by J Culbertson, H Krous, R Bendell. (Pp 264+xix; £29.95 hardback.) Edward Arnold, 1988. ISBN 0-340-49381-6.

In contrast to the recent preoccupation with the role of suffocation in the sudden infant death syndrome (SIDS) both in the medical

and lay press, the advent of this book should act to restore a balance. It provides a comprehensive summary of areas of research, attempting to elucidate the aetiology of this syndrome, which remains one of the unsolved medical mysteries of our time. The effect of the loss on the family is also closely examined as undoubtedly they should be considered as the surviving victims of this syndrome.

The first of two parts in this publication deals with the medical aspects of SIDS and infantile apnoea. The reader is first reminded of the epidemiology of the syndrome and how proposed theories attempt to match its particular epidemiological characteristics. Pathological findings are then described in much detail, the pathologist having the unique opportunity to study true SIDS victims, whereas other researchers have to rely on certain identified high risk groups in which the exact relationship with SIDS remains unclear. It would appear, however, that the positive findings of one particular pathologist are seldom confirmed by another, making it difficult to assess the significance of these potentially relevant discoveries. The wealth of cardiorespiratory investigation in this field, with particular emphasis on the possible role of infant apnoea, is then discussed. The work presented is stimulating and convincing but with no mention of the large prospective studies that have failed to identify apnoea as a predictive factor in infants subsequently dying with a diagnosis of SIDS.

The second part of this work concentrates on the impact that SIDS has on the family and how in this particular circumstance the grieving reactions experienced may be affected. Such reactions are frequently observed and identifiable, but being described and outlined so clearly by the authors serve to concentrate the reader's thoughts on the particular needs of these families. Attention is also paid to the surviving siblings in the family, a much neglected group.

The impact of having an infant with apnoeic spells and the effect of introducing a home monitor is also explored and worthy of study by any paediatrician who supplies apnoea monitors for home use. The need for continuous medical input and support to these families is emphasised.

One cannot but be impressed with the contribution that the parents of SIDS victims themselves have made in the instigation and organisation of SIDS research. They have needed to stimulate a rather slow and accepting health profession into action and their efforts continue to fund much of the ongoing research.

The list of contributors to this publication is impressive, as is the extensive list of some 700 references. The balance between investigative detail and commentary is about right to make it a useful and readable text for paediatricians and other health care workers who are involved with families that have been victims of SIDS. As with any work concerning sudden infant death syndrome it still leaves the reader with more questions than answers.

N RUGGINS
Research fellow

Garrod's Inborn Factors in Disease. Edited by Charles R Scriver, Barton Childs. (Pp 248; £25 hardback.) Oxford University Press, 1989. ISBN 0-19-261574-2.

All clinicians and scientists working in the field of inherited metabolic disease will be

familiar with the name of Sir Archibald Garrod. His Croonian lectures delivered at the Royal College of Physicians, London, in 1908 and which were followed by publication of his most famous work, *Inborn Errors of Metabolism*, introduced the concept of chemical individuality. What is not widely known, but elegantly described in this text, is Garrod's continuing contribution to medical science and in particular further development of his ideas on chemical individuality and diathesis, by which he meant an individual's genetic predisposition to disease.

Scriver and Childs have produced a delightful volume which will be of interest to a wide range of readers, not only those active in the genetic or metabolic fields. Using Garrod's lesser known text, *Inborn Factors in Disease* (largely ignored when first published in 1931, but reproduced here in full) they show Garrod to be a man of great vision with ideas that have application in these days of 'new' genetics.

The authors set the scene by describing the work of Garrod alongside that of his contemporaries. This is followed by a reproduction of the original text, *Inborn Factors in Disease*, with the addition of pertinent footnotes. To conclude the authors develop the ideas within the treatise to encompass more recent advances in genetics and molecular biology.

The end result is a stimulating book that can be read from cover to cover in only a couple of sittings. The ideas that the book generates take much longer to ponder over. There should be a place for this book in any medical library.

J E WRAITH
Senior registrar

Virological Infections. By Donald M McLean. (Pp 644; \$105.50 hardback.) Charles C Thomas, 1989. ISBN 0-398-05501-7.

To write a virology book at a time when new viruses are being discovered with amazing regularity provides considerable difficulties to the author.

This large book attempts comprehensive coverage of the field of both viral and chlamydial infections. Unfortunately it does not provide enough information for the paediatrician who may have to deal with serious viral infection both in the newborn baby and older child. The book starts with a most interesting historical introduction of development of diagnostic techniques in virology and includes a description of recombinant technology. It then goes on to describe the classification of viruses and laboratory techniques in viral identification. There is a useful section on the pathogenesis of virus infections followed by a chapter on vaccines and antiviral substances. I would have liked a rather fuller section on the immunological response to viral infection.

There then follows a description of the different viruses and the infections that they cause and the last part of the book is divided into sections on central nervous system, virus infections, respiratory virus infections, exanthemata, generalised febrile illnesses, and gastroenteritis.

There is no doubt that this book is comprehensive and there were no viruses omitted from the text. The neonatologist looking for details of management of herpes simplex infection during pregnancy and after delivery would be disappointed by the sparseness of detail. Although the author has gone into the literature in considerable detail, some of what

is quoted is no longer believed. Thus the statement that congenital varicella syndrome develops in 9% of infants born to mothers who became infected during the first trimester is no longer considered to be true. If this sort of information were transmitted by a virologist to his obstetrician or paediatrician then potentially misleading advice may be given to the mother resulting in an unnecessary termination for instance. When it comes to discussion of the mother with varicella at the time of delivery there is no information given as to the use of zoster immune globulin in the newborn baby to protect from potentially fatal disease.

I was disappointed that there was no information on the use of interferon analysis on the diagnosis of viral infections such as encephalitis and perhaps there is too little advice in the book as to how certain diseases should be investigated by the clinician.

I do not feel that this is a book that should be on the book shelf of the paediatrician or even that of the virologist who may be advising the paediatrician on what action to take once a diagnosis of viral infection has been made.

P T RUDD
Consultant paediatrician

Catalog of Prenatally Diagnosed Conditions. By David D Weaver. (Pp 251; £29 hardback.) The Johns Hopkins University Press, 1989. ISBN 0-8081-3771-5.

This book is a testimony to the maxim 'good things come in small packages'. To anyone working in the various fields of prenatal diagnosis, the difficulty in extracting from the literature whether or not a particular condition has been diagnosed in pregnancy is well known. Professor Weaver has provided an excellent reference work to such disorders.

The main text is surprisingly short (151 pages) but this is a tribute to its conciseness. It consists of a logical layout of chapters including chromosomal abnormalities, congenital malformations and related disorders, dermatological disorders, fetal infections, haematological disorders, inborn errors of metabolism, others, and tumours and cysts. 'Others' is a mixed bag, ranging from headings such as 'fetal distress' to mendelian disorders, such as cystic fibrosis and Duchenne muscular dystrophy. This section may need further rationalisation as the book expands, as it surely will.

Within each chapter, the various disorders are listed both numerically according to a PD (prenatal diagnosis) number and also alphabetically, which will allow for logical expansion. The inclusion of the various alternative names and the McKusick catalogue number (when one is available) are useful.

For each condition, one or more methods used to diagnose the disorder are given, together with aspects of the condition which they detect (for example, absence of fetal movements in arthrogryposis on ultrasonography), with references. Other useful comments are added, including the preferred method of diagnosis, when known. Various superscripts define, for example, when in the pregnancy the findings were noted. Careful attention to the introductory statements on the use of the book and the meaning of the superscripts are vital to obtaining the maximum benefit from the book. The index provides some useful differential diagnoses, for example, of oligohydramnios.

The only obvious drawback of the book is

that in such a rapidly expanding field, it is soon out of date. Perhaps it would lend itself to being in the form of a computerised database, with regular updates for subscribers.

It is difficult to gauge from the book itself the reliability of a given test; this however, can be assessed from studying the references.

Any conditions which have not been diagnosed prenatally before are simply not referred to, leaving the reader with a slight feeling of uncertainty. Nevertheless, the logical layout of the text and the index help in this regard.

I would highly recommend the book as a useful addition to the libraries of clinical geneticists, obstetricians, paediatricians, and others with an interest in the field of prenatal diagnosis.

E M THOMPSON
Consultant clinical geneticist

Pediatric Neurosurgery. Surgery of the Developing Nervous System. 2nd ed. Edited by Robert McLaurin, Joan Venes, Luis Schut, Fred Epstein. (Pp 604; £93.75 hardback.) W B Saunders Company, 1989. ISBN 0-7216-2748-X.

The second edition of this volume, like its predecessor, has been produced under the auspices of the paediatric section of the American Association of Neurological Surgeons. The increased size of the book reflects a growing awareness of the pathophysiological changes that may occur in the developing nervous system and the application of newer diagnostic and therapeutic techniques to paediatric neurosurgery. Despite its 72 contributors, the book is cohesive and almost uniformly excellent in its approach, in short, a tour de force of editorship. There has been rapid expansion in the field of paediatric neurosurgery in the past decade, and the editors have set out to fulfil the need for updated information that such progress creates. There is little doubt that the book admirably fills this ecological niche.

The volume provides a detailed account of the current state of the art of paediatric neurosurgery. Each chapter has been revised, many significantly expanded—for instance, the tethered spinal cord, interventional radiology, and craniofacial surgery—and there are several additional chapters including those on ethics, neurooncology, and stereotactic procedures. Although there is a wealth of detail on the 'how?' for the practising neurosurgeon, one does not need to look elsewhere for the 'why?' as the text takes the reader through the

extensive and often contradictory literature of each particular topic with critical discussion. The chapters on the surgical management of childhood epilepsy were of particular interest and gave a clear perspective on this topical subject, the large section on central nervous system neoplasms was comprehensive, whereas the chapters on movement disorders and childhood stroke were a little more eclectic. If one were to quibble, then perhaps the chapters on head trauma would have benefited from some discussion of the coma scale and although intracranial pressure monitoring is mentioned, criteria for its use are not suggested.

The quality of the illustrations and reproduction of the neuroradiological imaging is what impresses the reader immediately. Among the 400 illustrations there was none that did not have a clear message. The text is attractively presented and adequately referenced, although citations beyond 1985 were infrequent in some chapters.

This book will be of value to all paediatricians, anaesthetists, radiologists, and those in intensive care looking after children with neurological disease or injury and should certainly be available in the library. For the paediatric neurosurgeon and paediatric neurologist it is likely to join the select collection of favoured books that all physicians like to keep within easy reach for frequent reference. It is expensive but has that indefinable quality of the book that is a pleasure to own.

G F COLE
Consultant paediatric neurologist

Perinatal Brain Lesions. Edited by Karen E Pape, Jonathan S Wigglesworth. (Pp 279; £35.00 hardback.) Blackwell Scientific Publications, 1989. ISBN 0-86542-028-9.

This work is one of a series of five books entitled *Contemporary Issues in Foetal and Neonatal Medicine*. This is a well written account of different aspects of perinatal brain damage outlining the current state of knowledge in diagnosis and management of brain lesions in newborn infants. The 14 authors cover specific areas in which they enhance our understanding of pathogenesis, evolution, and outcome of perinatal brain lesions.

The first chapter deals with the pathology of the most common perinatal hypoxic-ischaemic brain lesions in the perspective of the developmental state of the premature brain. In the second chapter the application of computed tomography in diagnosis of brain lesions in newborn infants is described and shortcom-

ings and limitations of this method of investigation are outlined. Chapter 3 describes the application of cranial sonography in perinatal investigation of cerebral lesions. Sonographic examination supplies a reliable diagnosis of intracranial haemorrhage but some limitations are encountered in the diagnosis of cerebral infarction. Therefore correlation between sonographic findings, other modalities of imaging, and neuropathological examination is essential. Different types of scanners available with their advantages and disadvantages are analysed. A brief chapter on birth asphyxia delineates at a cellular level the pathophysiology of perinatal hypoxic-ischaemic encephalopathy. The chapter on experimental models of intraventricular haemorrhage includes a description of animal models in which intraventricular haemorrhage occurs spontaneously and contrasts it with animal models in which intraventricular haemorrhage is produced artificially. The influences of the results derived from animal studies on management of human disease are discussed. The chapter on techniques for studying cerebral perfusion gives a detailed insight into the physiology and regulation of the cerebral blood flow and compares the non-invasive with invasive methods of investigation and monitoring of cerebral perfusion in human newborn infants. The next two chapters deal with prevention, management, and monitoring of the germinal layer intraventricular haemorrhage, and post-haemorrhagic hydrocephalus. In a chapter on the follow up of high risk infants the authors describe poor predictability of the outcome of perinatal brain injury. It is not known why some infants will develop normally despite having brain injury and some become handicapped. This question is addressed in the last chapter of the book where an attempt is made to explain this unpredictability on the basis of plasticity of the developing human and animal brain. The apparent discrepancy between the size of lesions and the extent of neurological impairment can be at least partially explained by environmental influences on cell growth and organisation in the developing central nervous system.

I found the book worthwhile and easy to read, partly due to concise format and clearly presented context. The chapters are adequately illustrated and well referenced. I would recommend this book to neonatologists, perinatal pathologists, and neuropathologists involved in examination of infants' brains as a specialised but not over complex summary of important findings in the field of perinatal brain lesions.

I E MOORE
Consultant histopathologist

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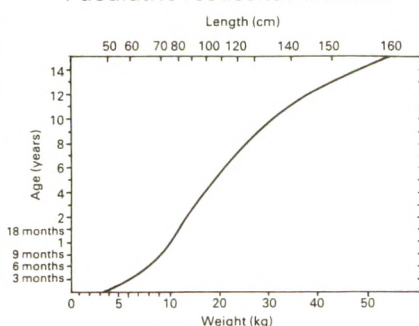
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Endotracheal tube

Length (cm)	Internal diameter (mm)
18-21	7.5-8.0
18	7.0
17	6.5
16	6.0
15	5.5
14	5.0
13	4.5
12	4.0
10	3.5
10	3.0-3.5

Paediatric resuscitation chart



Adrenaline (ml of 1/10 000) intravenous or endotracheal	0.5	1	2	3	4	5
Atropine (mg) intravenous or endotracheal	0.1	0.2	0.4	0.6	0.6	0.6
Bicarbonate (ml of 8.4%) intravenous	5	10	20	30	40	50
Calcium chloride (mmol)* intravenous	1	2	4	6	8	10
Diazepam (mg) intravenous per rectum	1.25 2.5	2.5 5	5 10	7.5 10	10 10	10 10
Glucose (ml of 50%) intravenous	10	20	40	60	80	100
Lignocaine (mg) intravenous or endotracheal	5	10	20	30	40	50
Salbutamol (µg) intravenous	25	50	100	150	200	250
Initial DC defibrillation (J)	10	20	40	60	80	100
Initial fluid infusion in hypovolaemic shock (ml)	50	100	200	300	400	500

* One millilitre calcium chloride 1 mmol/ml = 1.5 ml calcium chloride 10% = 4.5 ml calcium gluconate 10%

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ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the British Paediatric Association

Annotations

397 Pathogenesis and management of aspergillosis in cystic fibrosis *E J Hiller*

399 Management of threadworm infestation during pregnancy *F N Leach*

Original articles

401 How much aerosol reaches the lungs of wheezy infants and toddlers? *B Salmon, N M Wilson, M Silverman*

404 Nebulised sodium cromoglycate in infancy: airway protection after deterioration *C O'Callaghan, A D Milner, A Swarbrick*

407 Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home *N M Wilson, M Silverman*

411 Food and drug reactions, wheezing, and eczema in preterm infants *A Lucas, O G Brooke, T J Cole, et al*

416 Neurotoxicity in lymphoblastic leukaemia *J M Chessells, T C S Cox, B Kendall, et al*

423 The sexually abused battered child *C J Hobbs, J M Wynne*

428 Surveillance for anaemia: risk factors in patterns of milk intake *A F Mills*

432 Oculokinetic perimetry for the assessment of visual fields *B J Clark, C Timms, W A Franks*

435 Postmortem demonstration of intrapulmonary arteriovenous shunting *M J Wilkinson, D G Fagan*

438 Role of aortopexy in the management of primary tracheomalacia and tracheobronchomalacia *P S Malone, E M Kiely*

441 Response to treatment of congenital adrenal hyperplasia in infancy *M C Young, I A Hughes*

445 Symptoms and transmission of intestinal cryptosporidiosis *M Egger, D Mäusezahl, P Odermatt, et al*

448 Treatment of constitutional delay of growth and puberty with oxandrolone compared with growth hormone *A Buyukgebiz, P C Hindmarsh, C G D Brook*

449 Endotracheal compared with intravenous administration of atropine *R F Howard, R M Bingham*

451 Five year outcome of preterm sextuplets related to size at birth *N Marlow, A M Ellis, B J Roberts, et al*

Personal practice

453 Treatment of epilepsy in people with multiple handicap *H Foley*

Regular review

457 The human genome: a prospect for paediatrics *R M Gardiner*

Current topic

462 Choice of sleeping position for infants: possible association with cot death *A C Engelberts, G A de Jonge*

468 Letters to the editor

ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the British Paediatric Association

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ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the British Paediatric Association

Annotations

Pathogenesis and management of aspergillosis in cystic fibrosis

Aspergillus is a common genus of mould that grows on decaying vegetable matter, liberating its spores into the air all the year round but especially in the winter months. The spores are only about 3 microns diameter and can easily penetrate the bronchial tree. Where there is obstructive airways disease and impaired clearance mechanisms, as in cystic fibrosis, the fungus can proliferate and may be cultured from the sputum occasionally. In many patients this does not appear to cause any symptoms but in some it may lead to significant lung disease. The main species causing problems is *Aspergillus fumigatus*. It may colonise pre-existing lung cavities, especially those due to old tuberculosis, producing an aspergilloma. This leads to chronic cough and haemoptyses and radiographically presents as a mass surrounded by a crescent of air in a thick walled cavity. The fungus can spread rapidly in immunocompromised patients leading to an invasive aspergillosis which may prove rapidly fatal. Both these forms of infection have been described in patients with cystic fibrosis but are very unusual. The major problem in cystic fibrosis is allergic bronchopulmonary aspergillosis in which tissue damage is due to the immune reaction of the host.

Allergic bronchopulmonary aspergillosis

The first patients described were adults with asthma who developed recurrent episodes of pulmonary infiltrates and segmental or lobar collapse, associated with eosinophilia and the production of brown sputum 'plugs' containing *A. fumigatus*.¹ These episodes appeared to be followed by the development of proximal bronchiectasis at the site of the infiltrates.² There is evidence of both type I and type III immune responses with the production of IgE and IgG antibodies.³ The pathology is that of bronchiectasis with inspissated mucus containing fungal hyphae, eosinophils,

and mononuclear cells in the bronchi—the condition called mucoid impaction. The hyphae do not invade the tissue but may be surrounded by necrosis or chronic inflammation and areas of eosinophilic pneumonia.⁴ Lung biopsy is not needed to make the diagnosis, which can be established by demonstrating six of the criteria shown in the table.⁵

Diagnosis of allergic bronchopulmonary aspergillosis in cystic fibrosis

Allergic bronchopulmonary aspergillosis was first described in two children with cystic fibrosis in 1965.⁶ Since then it has become a well recognised complication of cystic fibrosis with an estimated incidence of up to 11%.^{7, 8} Allergic bronchopulmonary aspergillosis is possibly underdiagnosed as the underlying disease itself may be associated with exacerbations of cough and wheeze and there may be infiltrates on the chest radiograph. In practice, it is often diagnosed in patients with cystic fibrosis when an infiltrate fails to clear with antibiotic treatment appropriate to bacteria cultured from the sputum, and it should always be considered in this situation. The associated bronchial obstruction may lead to massive collapse of a lobe or whole lung.⁷ The radiographic findings may be of single or multiple infiltrates, often in the upper lobes. The lesions appear solid but computed tomography may show cavitation. They can occur in patients with any severity of cystic fibrosis including those with mild disease. Some patients have few, if any, symptoms—a recent child seen personally was found to have a large unsuspected opacity when a radiograph was taken for trauma. It is interesting to speculate how often such lesions may occur and resolve undiagnosed and what part they may play in the development of bronchiectasis.

Atopy and cystic fibrosis

Further problems arise in the diagnosis of allergic bronchopulmonary aspergillosis in cystic fibrosis, as in asthma, because of the known tendency of these patients to show some immunological response to *A. fumigatus*. Several cross sectional studies of groups of patients with cystic fibrosis have shown that about one third have circulating precipitins,⁹ and a similar number have positive skin tests to *A. fumigatus*, the incidence tending to be higher in older children and those with more severe disease.^{10, 11} The association of wheezing and of other atopic conditions such as hay fever and eczema is variable, as is a family history of atopy. Many patients with cystic fibrosis do wheeze,

Criteria for the diagnosis of allergic bronchopulmonary aspergillosis

<i>Major</i>
Reversible bronchoconstriction
Blood eosinophilia
Pulmonary infiltrate(s)
Positive immediate skin test reaction to <i>A. fumigatus</i> extract
Raised serum IgE concentration
Specific IgE to <i>A. fumigatus</i> by radioallergosorbent test (RAST)
Positive serum precipitins to <i>A. fumigatus</i>
Central bronchiectasis

<i>Minor</i>
Positive sputum culture for <i>A. fumigatus</i>
Brown plugs in sputum
Late skin test reaction

especially with infections, but often have a poor bronchodilator response and lack the classical bronchoconstriction after exercise that is seen in children with asthma.¹¹ Bronchial provocation tests with *A. fumigatus* extract in a small number of patients with cystic fibrosis and with positive skin tests, however, gave a positive immediate result in four patients, two of whom had a dual reaction and had troublesome cough and wheeze for some days after the test.¹² This suggests that *A. fumigatus* may be causing appreciable symptoms in some patients with cystic fibrosis without producing the complete picture of allergic bronchopulmonary aspergillosis, which may parallel the seropositive phase, without radiographic evidence of lung damage, that is described in asthma.¹³

Management and outcome

Allergic bronchopulmonary aspergillosis that has been proved should be treated with oral steroids. Prednisolone 0.5–1 mg/kg/day leads to rapid resolution of symptoms and of the opacity and a fall in the total and specific IgE concentrations within weeks.⁵ Some authors recommend continuing treatment at a lower dose for a month, six months, or longer until the IgE concentration plateaus, but there are no controlled trials or long term studies comparing different regimes in cystic fibrosis. Inhaled steroids or sodium cromoglycate may improve symptoms but do not prevent recurrent infiltrates,¹⁴ which are very variable in frequency and severity. There are no long term follow up studies of patients with cystic fibrosis and allergic bronchopulmonary aspergillosis, but in a group of 12 children who had it with asthma there were seven exacerbations detected in three patients over six years.¹⁵ Personal experience of a few patients and anecdotal reports from others suggest that some patients with cystic fibrosis have recurrences of allergic bronchopulmonary aspergillosis over two or three years but tend to settle after that time and do well in the long term—or, at least, no worse than other patients with cystic fibrosis. Bronchiectasis, often with the 'fingerglove' appearance of mucoid impaction, is usually apparent radiographically when the opacity clears but in time becomes much less prominent and tends to merge into the background lung disease so that it is difficult to know how much it has contributed. Severe pulmonary damage has been described in adults with asthma,¹⁶ however, and there is clearly a risk that this may occur in cystic fibrosis, leading to an increased rate of loss of lung function.

There is sometimes reluctance to use steroids in cystic fibrosis because of the presence of bacterial infection, but in practice it does not seem to lead to spread of infection and there is some evidence that it may actually be helpful by suppressing damaging immune reactions.¹⁷ Long term steroid treatment, however, has well known complications and posterior subcapsular cataracts have recently been described in patients with cystic fibrosis on prednisone for allergic bronchopulmonary aspergillosis, which appeared unrelated to the dose or duration of treatment.¹⁸

Antifungal drugs have not been used in the past because inhaled treatment, such as dyes and natamycin, seemed ineffective and allergic bronchopulmonary aspergillosis was not thought to warrant the side effects of amphotericin. With the introduction of oral drugs such as ketoconazole and itraconazole, interest in this form of treatment revived and there have been occasional reports of benefit in indi-

vidual patients. A small controlled trial of ketoconazole in patients without cystic fibrosis but with allergic bronchopulmonary aspergillosis showed an improvement in symptoms and fall in specific IgG during treatment compared with placebo.¹⁹ No side effects were seen, but the trial was abandoned when reports of serious liver damage due to ketoconazole were published.²⁰ Very little information is available yet about itraconazole. For the present the use of antifungal drugs does not seem to be warranted as a rule but might be considered in a patient who has significant steroid side effects or uncontrolled symptoms.

Avoidance of *A. fumigatus* does not seem feasible though it is wise to make sure that nebulisers and other equipment are kept clean and dry to prevent fungal contamination. Of five children with allergic bronchopulmonary aspergillosis recently reported from Dublin, however, only one was using a home nebuliser.⁸ Its incidence does not seem to increase significantly in older patients with cystic fibrosis. It is a condition that needs to be considered regularly, investigated appropriately, and treated promptly with steroids, both to improve symptoms, if any, and to prevent long term lung damage.

E J HILLER

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I would like to thank Dr Denis Shale for helpful advice.

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Management of threadworm infestation during pregnancy

Parasitic worms commonly engender feelings of disgust 'in the eye of the beholder', and when the beholder is pregnant, such feelings are likely to be particularly acute. Threadworm infestation (enterobiasis), unless overwhelming, is not usually considered a serious threat to health, although it has been blamed for a wide variety of maladies. These considerations aside, the condition is aesthetically unpleasant and can lead to acute anal irritation or pain that may interfere with sleep and prove socially embarrassing. Experience gained in a drug advisory service suggests that the problem of threadworm infestation during pregnancy is frequently encountered in medical practice and it is hoped that the following brief overview will provide some help to the prescriber.

The true incidence of threadworm (*Enterobius vermicularis*) infestation among the adult population is unknown but reputed improvements in the social conditions of the population do not appear to have significantly impeded threadworm survival. Its life cycle is well described (albeit not completely unravelled) and a detailed account would be inappropriate for this article. Suffice it to comment that the threadworm (during its nocturnal excursions) deposits very large numbers of eggs upon the perianal skin causing the host intense irritation; the latter effect is partly attributable to the adhesive used for egg attachment. The act of scratching traps ova beneath the finger nails and, if personal hygiene is wanting, reinfestation occurs by oral ingestion. The duration of this cycle is approximately four to six weeks.

Faced with the pregnant patient, who is simultaneously infested with threadworms, the choice of drug is rendered difficult by a relative lack of data combined with overtones of fetal hazard.

Piperazine

Piperazine (Antepar, Wellcome; Pripsen, Reckitt and Colman) is readily absorbed from the gastrointestinal tract and in the case of *Ascaris lumbricoides* is known to block the stimulant action of acetylcholine at the myoneural junction. Succinate production is also inhibited. Curiously its mode of action against threadworms has not yet been established. Although piperazine has a long history of use reports of associated teratogenicity are sparse (personal communication, Reckitt and Colman),¹ although details of two possibly relevant cases have been reported to Reckitt and Colman. In one instance a baby with bilateral hare lip, cleft palate, and anophthalmia, was born to a mother who had taken Pripsen at 12 and 14 weeks' gestation. The remaining incident involved an infant with an abnormality of the right foot whose mother had taken Pripsen at six and eight weeks of pregnancy. These reports have led to a revision of data sheet recommendations, current advice being to avoid use during the first trimester and preferably to delay treatment until after parturition. A further, perhaps theoretical consideration, is that piperazine is potentially neurotoxic, although this is unlikely to be a problem at normal dosage in patients with adequate renal function. Any effects upon the fetal neural system remain a matter of speculation and have not, to date, been demonstrated clinically. In view of the fact that piperazine is excreted in breast milk, the manufacturers advise that the infant recipient should be fed immediately

before maternal dosing; breast feeding should then be avoided for the next eight hours during which the milk should be expressed and discarded.

Mebendazole

Mebendazole (Vermox, Janssen) is, in contrast to piperazine, poorly absorbed from the gastrointestinal tract. Although its exact mode of action in susceptible helminths (of which there are many) remains unknown, it appears to induce selective and irreversible inhibition of glucose uptake thus producing 'diabetic' worms. Its poor gastrointestinal absorption should provide fetal protection. Studies in the rat, however,² have revealed both teratogenic and embryotoxic tendencies on the part of mebendazole (as well as an ability to induce kinky tails in mice offspring³). The manufacturers of the drug have received several reports of dysmorphogenic effects associated with its use in human pregnancy, although of a range and rate of incidence which are comparable with control values (personal communication). This evidence has prompted warnings against its use during gestation. Evidence that mebendazole can inhibit lactation is based on a single case report and it is unlikely that it reaches breast milk in significant amounts.

Pyrantel

Pyrantel (Combantrin, Pfizer) is a depolarising neuromuscular blocking agent that acts by causing the release of acetylcholine and inhibiting cholinesterase. It has a long history of use in developing countries but there is little if any evidence regarding its use during pregnancy or lactation. Despite one report suggesting that pyrantel can be used safely in pregnancy,⁴ and evidence that it is poorly excreted in breast milk,⁵ the lack of data dictates caution. Like mebendazole, pyrantel is poorly absorbed from the gastrointestinal tract and has a wide safety margin.

Thiabendazole

Thiabendazole (Mintezol, Merck Sharp and Dohme) has an extremely wide range of anthelmintic action and is therefore a favourite for treating mixed worm infestation; it is readily absorbed from the gastrointestinal tract. There is animal evidence that it is embryotoxic,^{6,7} and a study of its use in late human pregnancy has shown a higher incidence of nausea, vomiting, and giddiness than in non-pregnant controls.⁸ Altogether 90% of an ingested dose of thiabendazole is excreted within 48 hours and this would be a reasonably safe interval to wait before the resumption of breast feeding after taking a dose.

Bearing in mind the obvious limitations of the available anthelmintics, the counsel of perfection in dealing with the pregnant threadworm sufferer is to attempt a rigid regimen of personal hygiene. This measure should, if the facts of threadworm life are to be believed, lead to 'natural' eradication. The mother to be should be asked to vigorously scrub both hands and nails after each bowel evacuation and to take daily baths with particular attention to perianal hygiene. Pyjamas rather than a nightdress are recommended and night attire and clothes should be washed daily. At the same

time, other members of the family who may be reservoirs of infection, should receive appropriate drug treatment. The opportunity might be taken to explain the grounds for reser- vation concerning systemic treatment. If immediate eradica- tion is considered important and/or 'natural' eradication is problematic, piperazine would be a reasonable choice, delaying wherever possible to at least the end of the first tri- mester. Should perianal irritation cause lack of sleep, judi- cious use of a soothing cream may be helpful.

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F N LEACH

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ORIGINAL ARTICLES

How much aerosol reaches the lungs of wheezy infants and toddlers?

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Abstract

Using sodium cromoglycate as a non-toxic marker, we assessed the delivery of aerosol to nine wheezy infants and seven healthy adults. The drug was delivered to the infants by face mask and spacer device from a metered dose inhaler, and by face mask and nebuliser to the infants and the adults who breathed through their noses. The concentration of sodium cromoglycate was estimated in timed urine collections to find out how much of the dose was absorbed from the lung. Only 0.13% to 0.61% of the 20 mg nominal dose was detected in the urine, representing an estimated 0.3% to 1.5% deposited in the lung. Nasal filtration of aerosol could be a critical factor in reducing lung deposition.

Many therapeutic trials of inhaled drugs for the treatment of asthma in wheezy infants and toddlers have failed to show any appreciable beneficial effects. An essential step in understanding why this is so, is to find out if enough drug reaches the target organ. In adults under optimum conditions only about 14% of an inhaled dose reaches the lungs.^{1 2} Most studies entail inhalation of a radiolabelled marker, or require invasive procedures such as serial venepunctures. Because of this, objective information on pulmonary drug deposition in young children has not been available.

Assay of sodium cromoglycate in plasma has been used as a means of assessing inhaled drug delivery in adults. It is safe and free from side effects. Its pharmacokinetics after inhaled, intravenous, and oral administration have been investigated extensively in adults.^{2 3} It is water soluble and remains in the extracellular compartment, predominantly in the ionised form at physiological pH. Sodium cromoglycate is absorbed efficiently from the respiratory tract. In contrast, less than 1% of an oral dose is absorbed from the gastrointestinal tract. Once absorbed it is not metabolised and is rapidly cleared from plasma. There are two routes of excretion: renal and biliary. Quantitatively they are of roughly equal importance, 43% of the absorbed dose being excreted in the urine. Radioimmunoassay of the unchanged drug in plasma and urine can be done.⁴

In a small pilot study we established that after treatment of young children we could detect sodium cromoglycate in urine. There are no data on its pharmacokinetics in young children.

The aim of this study was to assess the amount of drug deposited in the respiratory tract of young children using urinary excretion

of sodium cromoglycate as the marker. We compared two methods of administration—jet nebuliser and metered dose inhaler with a valved spacer device—and compared the results in children with an assessment of the respiratory deposition of sodium cromoglycate in seven adults using the same jet nebuliser and methods. The latter comparison allowed us to test the assumption that the pharmacokinetics of sodium cromoglycate were similar in infants and adults. We did not use the face mask and valved spacer in the adults because this method of administering the aerosol is not commonly used in that age group.

Subjects and methods

We studied nine boys aged between 9 and 36 months (median 16). All had frequent and recurrent wheezy episodes but were well when they attended the outpatient department on the two study days. Boys were chosen because it was easier to collect urine samples from them.

On one study day the treatment was by an Acorn nebuliser (Medic Aid) driven by compressed air at 8 l/minute. Sodium cromoglycate respirator solution (20 mg diluted to 4 ml with normal saline) was nebulised for 10 minutes and administered during tidal breathing using a Hudson oxygen facemask (Henleys Medical Supplies) held against the face. On the other study day the same dose of sodium cromoglycate (four puffs of Intal-5) was given from a metered dose inhaler into a multispace (Medic Aid). This has lightweight inspiratory and expiratory valves, which are protected by a shield from clogging up with powder. The proximal end was attached to a facemask with a cushioned rim (Medic Aid) and applied firmly around the nose and mouth to achieve an airtight seal. The infant took several breaths from the spacer for each actuation of the metered dose inhaler.

The order of administration was random. As soon as control urine samples had been obtained treatment was given. Timed serial urine samples were collected into 24 hour collecting bags, which were checked at frequent intervals and drained as soon as the parent or investigator noted that urine had been passed. Urine volumes were recorded. Leakage was measured by recording the change in weight of the pre-weighed nappy.

A single study was carried out using the Acorn nebuliser and facemask in seven healthy adults. Using the same dose and protocol, they inhaled sodium cromoglycate and collected urine samples at 1, 2, 3, 4, 6, and 8 hours. They

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Cumulative urinary excretion of sodium cromoglycate at four hours

	Children		Adults	
	Spacer	p Value	Nebuliser	Nebuliser
Median (μ g)	26	<0.05	66	130
Range	17-55		25-270	70-381
Median percentage of 20 mg nominal dose	0.13		0.33	0.65

were instructed to use tidal nasal breathing from the facemask.

An aliquot of each urine sample was frozen. Analysis was carried out on coded samples by radioimmunoassay, the technician being unaware of when the specimen had been taken.

ANALYSIS

Obviously the infants did not void to a time schedule and to compare subjects it was necessary to interpolate a value for a given arbitrary time point. Cumulative urinary excretion of sodium cromoglycate was plotted against time. Most curves were approaching a plateau by four hours, so this time was taken. For each subject, data were plotted in two ways: firstly, they were fitted to a rectangular hyperbola assuming first order pharmacokinetics for excretion of sodium cromoglycate,³ and secondly they were plotted by joining adjacent time points but making no assumption about drug kinetics. There was excellent agreement between the methods. The values reported here are based on the first method. Wilcoxon's rank sum test was used to compare the two modes of administration of sodium cromoglycate for children, and the Mann-Whitney U test for comparison of results of data from adults and children.

Results

Analysis of cumulative excretion curves indicated that over 90% of the final total had been excreted by four hours in both infants and adults.

The cumulative urinary excretion of sodium cromoglycate at four hours was significantly greater when the children were treated with nebuliser than with a spacer ($p < 0.05$). After nebulisation the urinary excretion was significantly greater in adults than in children ($p < 0.05$) (table). The amount excreted was a minute proportion of the nominally delivered dose. There were wide individual differences: one child and one adult given nebulised sodium cromoglycate excreted more than double the maximum of the other subjects in their group. We learned afterwards that the adult concerned had in fact breathed orally during the study instead of, as instructed, breathing nasally. We can only speculate on the chosen route of inhalation of the infants, but suspect that as they were settled and cooperative they breathed nasally most of the time.

Discussion

Sodium cromoglycate is efficiently absorbed from the respiratory tract, but only 0.8% of an

oral dose is absorbed from the gastrointestinal tract.^{2,3} The area under the curve for plasma concentrations of sodium cromoglycate after inhalation correlates well with its urinary clearance, and plasma concentrations increase with doses within the range 2-20 mg.⁵ Its action is not related to its plasma concentrations, which is an indication of the amount absorbed and thus indirectly of the amount actually delivered to the respiratory tract.

In adults 43% of an intravenous dose of sodium cromoglycate is excreted unchanged in the urine within 90 minutes.² In our study of seven healthy adults breathing through their noses we calculated that only 1.5% of 20 mg of sodium cromoglycate was absorbed after delivery by nebuliser and face mask. This lends support to the argument that the delivery system is a limiting factor in the efficient delivery of the drug to infants.

Although there are no data concerning the pharmacokinetics of sodium cromoglycate in young children, there is no theoretical reason why it should differ from adults. If we speculate that the urine:plasma ratio is the same in young children as it is in adults we can calculate that for the nebuliser 0.76% of the nominal dose of 20 mg of sodium cromoglycate was absorbed. In proportion to body size this represents a larger effective lung dose than for adults. For the spacer, the equivalent value was 0.30%. Even if only 70% of the drug that was deposited on the respiratory mucosa was absorbed,³ it is clear that delivery of sodium cromoglycate to the respiratory tract was low whichever method of inhalation was used.

A proportion of the nebulised dose must have been swallowed. Even if only 0.8% of this were absorbed, the quantity could have contributed appreciably to the sum excreted, leading to an overestimate of the dose absorbed from the respiratory tract. Thus the true dose delivered may have been even lower.

How much can we generalise from data collected using one specific jet nebuliser and one particular valved spacer? The Acorn nebuliser, run at 8 l/minute, has an output of 0.34 ml/minute and a mass median aerodynamic diameter of 4.5 microns (D Cameron, M Clay, personal observations). These figures are close to the ideal for therapeutic aerosols. The spacer was probably less than ideal. Its output was only 27% of that of a more widely used device (Nebuhaler, Astra) when they were assessed in vitro using a multistage impinger with a flow rate of 60 l/minute (A Clark, personal observations). This is, however, greater than the flow rate that a toddler will generate under tidal breathing conditions. Using a more efficient spacer, the lung dose absorbed after delivery by

metered dose inhaler and spacer might have been greater. Our choice of spacer was determined by the fact that the Medic Aid spacer has lightweight inspiratory and expiratory valves, and has an easily attachable airtight face mask. The use of a sealing facemask attached to a Nebuhaler (Astra) with the inspiratory valve held open by gravity had been described for delivery for aerosols to infants.⁶ The amount of drug reaching the lungs using this device has not, however, been reported.

Obviously there is wastage of the drug; a residue is left in the nebuliser or spacer and some escapes into the atmosphere during expiration. We attempted to measure the former but our measurements were unreliable, because a surfactant in the propellant interfered with the drug assay.

If sodium cromoglycate can be absorbed from the nasal mucosa in infants breathing nasally, our data will have overestimated pulmonary deposition of sodium cromoglycate. Adults were asked to breathe through their noses to mimic the infants' pattern. Interestingly, the one subject who did not do so, and breathed through his mouth instead, had the highest value for urinary excretion of sodium cromoglycate. The estimated lung dose for that subject was 4.4% of the nominal dose. It seems likely that the nose acts as a filter, reducing pulmonary deposition to about a quarter of the value obtained during mouth breathing.

We conclude that sodium cromoglycate is a useful and safe marker of respiratory tract deposition in children and that it can be used to

compare the efficacy of different drug delivery systems. Though the nebuliser may have delivered more drug than the spacer and metered dose inhaler, the clinical importance of the difference is not clear. Toddlers and their parents seem to prefer the spacer to the more time consuming nebuliser. Delivery by either nebuliser or metered dose inhaler with spacer gave poor pulmonary deposition. It is therefore possible that some of the problems of treatment in young children are the result of inadequate amounts of the drug reaching the lungs. Improved techniques for drug delivery are needed to overcome the barrier imposed by the nose.

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Nebulised sodium cromoglycate in infancy: airway protection after deterioration

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Abstract

Over a two year period 100 infants with histories of wheeze were challenged with nebulised water. They were sedated and lung function measured by total body plethysmography. Thirteen of the 53 infants who developed bronchoconstriction after challenge with nebulised water were given nebulised sodium cromoglycate and rechallenged with nebulised water. All infants were initially challenged with normal saline, after which there was no significant change in lung function. After challenge with nebulised water and sodium cromoglycate there were significant decreases in specific conductance compared with those found after challenge with normal saline. After rechallenge with nebulised water there was no deterioration in lung function. Although sodium cromoglycate caused a deterioration in lung function in these infants, it protected their airways from challenge with nebulised water.

Nebulised sodium cromoglycate¹ and salbutamol² have little clinical effect on the airways of children under the age of 1 year. Recently, however, nebulised salbutamol has been shown to protect against the bronchoconstricting action of nebulised water in infants,³ but it may cause a transient paradoxical deterioration in the lung function of wheezy infants.⁴ The cause of this deterioration is not known, but may be associated with the acidity, preservatives, or osmolality of the nebulised solution, or with the drug itself.

The aim of this study was to assess how much nebulised sodium cromoglycate protected the airways of wheezy infants from challenge with nebulised water. The immediate reaction to the sodium cromoglycate nebuliser solution, which is hypo-osmolar was assessed.

Patients and methods

During an 18 month period 100 infants with

histories of wheeze were challenged with nebulised water. Thirteen of the 53 infants who developed bronchoconstriction after the challenge were entered into this study (table 1). At the time of the investigation two infants had mild wheeze. The others were clinically well and it was at least two months since their bronchiolitic illness. No infant had had an upper respiratory tract infection in the two weeks leading up to the study.

The infants were sedated with chloral hydrate 120 mg/kg and thoracic gas volume and airways resistance were measured by total body plethysmography as previously described.⁵ Baseline measurements of thoracic gas volume and airways resistance were made. Ultrasonically nebulised normal saline (21°C, volume 150 ml) from an intersurgical Variosonic nebuliser at setting 3 was given to the infants by face mask for two minutes at a flow rate of 5 l/minute. Thoracic gas volume and airways resistance were measured immediately after nebulisation and at five minute intervals until the readings were stable (defined as no change over a five minute period). A dense mist occasionally escaped from the space between the mask and the face in the first few seconds of nebulisation owing to an inadequate seal. The mask was readjusted and the study restarted with an adequate seal.

Infants were given ultrasonically nebulised water from the same nebuliser (21°C volume, 150 ml) for two minutes. Thoracic gas volume and airways resistance were again measured at regular intervals until readings were stable. The infants who developed signs of bronchoconstriction after being given nebulised water were given nebulised sodium cromoglycate through a Unicorn nebuliser chamber (Medic AID) (volume 2 ml of 1% sodium cromoglycate). A flow rate of 4.5 l/minute was maintained for five minutes. Thoracic gas volume and airways resistance were measured until stable.

Fifteen minutes after receiving the nebulised sodium cromoglycate the infants were chal-

Table 1 Details of 13 patients

Case No	Age (months)	Sex	History of confirmed respiratory syncytial virus bronchiolitis	Family history of atopy	Weight (kg)
1	3	Female	No	Yes	7.6
2	8	Female	No	Yes	8.5
3	4	Male	Yes	Yes	6.7
4	13	Male	Yes	No	12.0
5	12	Male	No	No	10.7
6	12	Male	No	Yes	9.2
7	19	Male	Yes	Yes	8.0
8	13	Female	No	Yes	10.2
9	9	Male	Yes	Yes	9.4
10	9	Male	No	Yes	10.4
11	6	Male	Yes	Yes	9.4
12	7	Male	Yes	No	9.9
13	12	Male	Yes	No	11.4

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The paired *t* test was used to evaluate the results. The study was approved by the Nottingham ethics committee and informed parental consent was obtained for investigations.

A 2 ml solution of 1% sodium cromoglycate was put into the reservoir of the Unicorn nebuliser chamber by pipette. The nebuliser was run for five minutes at 4.5 l/minute and the aerosol cloud was drawn into the impinger device by a vacuum pump. The amount of anhydrous sodium cromoglycate collected in the single stage impinger was estimated by a spectropho-

The mass median diameter of the nebulised water and saline cloud were again calculated by the Malvern laser particle size device on eight occasions. The output from the nebuliser was calculated by weighing the nebuliser tubes before and after nebulisation.

Oxygen saturation was not monitored continuously on paper during the study but did not drop below 80% at any time. The pH of nebulised sodium cromoglycate was 6.8, and the osmolality 60 mmol/kg. Normal saline had an osmolality of 280 mmol/kg and a pH of 6.7. The osmolality of sodium cromoglycate increased to 70 mmol/kg, and the osmolality of normal saline increased to 287 mmol/kg, after nebulisation.

The output of the nebulised saline and water are shown in table 2. The mass median aerodynamic diameter of sodium cromoglycate from the Unicorn nebuliser chamber (run at a flow rate of 4.5 l/minute) was 4.5 microns (geometric SD 2.5). The amount of sodium cromoglycate delivered in five minutes was 6.1 mg to the face



Table 2 Output characteristics of Variosonic nebuliser

	Mass median diameter (μm)	Geometric SD	Mean (SD) output/min (g)
Distilled water	5.0	1.7	1.9 (0.1)
Saline 0.9%	4.8	1.8	1.65 (0.11)

mask, and the amount of sodium cromoglycate lost from the nebuliser to the face mask was 1.8 mg.

Discussion

Challenge with nebulised water is a way of assessing bronchial reactivity in infancy. It enables us to assess the protective action of some of the drugs used in the treatment of asthma. The results of this study show that sodium cromoglycate protects the airways in infancy against the bronchoconstricting challenge of nebulised water. There was, however, transient bronchoconstriction after these infants were given nebulised sodium cromoglycate. We did not consider it ethical to sedate infants who were not ill for lung function studies, so we are unable to assess the effect of nebulised water or sodium cromoglycate in a control group.

Maximum bronchoconstriction in infants occurs during the first 10 minutes after challenge with nebulised water, and lung function has usually returned to the baseline measurement 15 minutes after challenge.³ The mechanism of water induced bronchospasm is not clear. Nebulised water increases lung epithelial permeability in both normal and asthmatic patients.⁶ In asthmatic patients, however, an increase in neutrophil chemotactic activity and histamine after challenge with nebulised water was found by Shaw *et al.*⁷

The sodium cromoglycate nebuliser solution caused transient bronchoconstriction in the lung function similar to that occurring after nebulised salbutamol is given.⁴ The sodium cromoglycate nebuliser solution is hypo-osmolar, which may be responsible for the bronchoconstriction. Interestingly, iso-osmolar nebulised sodium cromoglycate has been shown to provide better protection against methacholine and exercise induced bronchoconstriction in adults than the hypo-osmolar solution commercially available.⁸ In adults there have only been isolated reports of bronchoconstriction after challenge with sodium cromoglycate.^{9,10}

Because resistance to airflow increases inversely with the fourth power of the radius, the response to a bronchoconstricting stimulus could have a much greater effect on airflow resistance in the smaller airways of infants. There was a slight decrease in specific conductance compared with baseline values before challenge with water and before challenge with sodium cromoglycate. This may have augmented the response to the sodium cromoglycate. Nebulised water will also have reduced the tonicity of the airway secretions. This may have augmented the response to challenge with the hypo-osmolar nebulised sodium cromoglycate. Older children and adults with larger airways do not usually develop bronchoconstriction after nebulised sodium cromoglycate.

In contrast to our findings, Chung and Jones described the bronchodilator effect of sodium cromoglycate in children.¹¹ They found that sodium cromoglycate produced significantly raised peak expiratory flow rates before exercise, which reached a maximum immediately after exercise. Sodium cromoglycate was given in a nebulised form. These results suggest that nebulised sodium cromoglycate inhibits the action of exercise induced bronchospasm, and causes bronchodilatation at the same time.

Allegra and Bianco found that in adults sodium cromoglycate prevented bronchoconstriction produced by ultrasonically nebulised distilled water.¹² This was confirmed by Anderson *et al* in 1983.¹³ In our study nebulised sodium cromoglycate protected against the bronchoconstriction caused by nebulised water. It is unlikely that failure to induce bronchoconstriction with the second water challenge was the result of a refractory period following previous challenges. In a separate study of infants who developed bronchoconstriction after an initial challenge with water, only 20% were refractory to further challenges with water (unpublished observations). These results suggest that sodium cromoglycate must be reaching the lungs of these small infants.

The evidence that nebulised sodium cromoglycate does not work in infancy is sparse; it is our opinion that occasionally babies benefit from nebulised sodium cromoglycate. It is possible that with conventional nebulisers insufficient sodium cromoglycate enters the lungs. It is important therefore in future studies with nebulised sodium cromoglycate and other drugs in childhood that the particle size distribution of the aerosol delivered to the patient, and the amount of drug contained in various particle size fractions, is published with the results so comparisons between studies may more readily be made.

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Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home

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Abstract

In a double blind, controlled trial, the effect of high dose beclomethasone dipropionate (750 µg three times daily for five days) administered by metered dose inhaler and valved spacer, was compared with placebo, during 70 paired episodes of acute asthma in 24 preschool children. Treatment commenced at home at the first sign of an attack. Parents' blind preference for active treatment was significant. Data from 17 pairs of treatment, however, were affected by interventions such as hospital admission or oral corticosteroid treatment. These events occurred similarly in active and control periods. An intrasubject comparison was made of diary scores from the 18 pairs of episodes in which no intervention occurred in either the active or placebo treatment. Both daytime and night symptoms over the first week of the attack were significantly reduced by active treatment. Intermittent high dose inhaled beclomethasone dipropionate is beneficial in modifying the severity of acute episodic asthma in preschool children able to use a spacer device.

The large and increasing number of preschool children admitted to hospital with acute asthma is a clear demonstration that treatment is unsatisfactory in this age group.^{1,2} In conjunction with inhaled bronchodilator treatment, corticosteroids have been the mainstay of treatment for acute attacks. Storr and colleagues showed that for children over 2 years old, a single dose of prednisolone was significantly better than placebo in the treatment of acute asthma presenting at a hospital casualty department.³ A third of their steroid treated group, however, required further steroid treatment. Some young children develop acute attacks of wheezing every three to four weeks in the winter and there is an understandable reluctance to use oral corticosteroids so often.

In order to overcome the problem of frequent oral corticosteroid courses in young children this study was designed to assess the effect of treating acute attacks of asthma with a five day course of high dose inhaled topical steroids, using a spacer device. The aim was to start treatment at the onset of any symptoms suggestive of the beginning of an acute wheezing episode.

Patients and methods

PATIENTS

Thirty five children aged 1-5 years who had

experienced at least two episodes of acute wheeze in the preceding three months, were recruited from the children's outpatient departments of Hammersmith, Ashford, and Ealing hospitals (table 1). The attacks were of sufficient severity to require bronchodilator treatment during the night on at least two occasions per episode. An additional requirement was that the child could use a Volumatic spacer (Allen and Hanbury) satisfactorily. Daily prophylactic treatment, if used, continued unaltered.

TRIAL DESIGN

A double blind intrasubject comparison was made of the effect of treatment with beclomethasone dipropionate (250 µg/puff) and an identical placebo inhaler. The dose used was three puffs (by a Volumatic spacer) taken three times a day for five days, giving a daily total dose of beclomethasone of 2.25 mg. Children were given at least two puffs of a bronchodilator before each trial treatment. Trial inhalers were started at home when the parents recognised the first signs of an acute attack of asthma.

Each recruit was retained in the study until the next four acute episodes had occurred. The treatments were randomised in 'blocks' of two attacks, so that for each pair of attacks, one was treated with the active agent, and the other with the placebo inhaler. The treatment order was randomly determined.

Additional bronchodilator (up to eight puffs given over 10 minutes, or a nebulised aerosol) could be given as considered appropriate. In fact apart from the addition of the trial inhalers the parents and their doctors were encouraged to treat any ensuing symptoms as they had previously, with additional corticosteroids or hospital admission as considered necessary. Thus decoding was unnecessary at any stage during the study.

The parents were asked to record respiratory and systemic symptoms as well as additional treatment, for 14 days from the onset of each new attack, using the diary sheet provided. At the end of this time they recorded their opinion as to the effectiveness of the trial inhaler: helpful/did not help/don't know. The children were then examined in the outpatient clinic, so diaries could be checked and the next trial inhaler provided. For purposes of general management a note of any intercurrent symptoms was made in a separate diary. If any changes had been made to continuous prophylaxis between pairs of acute episodes, only the results obtained from pairs of treatments on the same day to day regime were used in the analysis.

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Table 1 Subject characteristics

Case No	Age (years)	Sex	No of attacks in previous 6 months	Admissions in past 1 year	Steroid courses in past 1 year	Prophylactic treatment	Home nebuliser*
1	1.6	M	5	11	1	Sodium cromoglycate	+
2	2.3	M	3	5	3	—	0
3	4.9	M	2	2	2	Inhaled steroids	0
4	2.5	M	2	2	2	Inhaled steroids	0
5	2.6	M	3	3	3	—	+
6	4.9	M	5	0	0	Inhaled steroids	+
7	4.6	M	5	0	1	Sodium cromoglycate	+
8	2.3	F	3	2	2	Inhaled steroids†	+
9	4.6	M	2	2	2	—	0
10	4.1	M	2	1	0	§	+
11	2.1	M	7	8	3	§	+
12	3.0	M	3	2	1	Sodium cromoglycate†	0
13	4.6	M	11	0	0	Sodium cromoglycate	+
14	3.1	M	4	2	2	Sodium cromoglycate†	0
15	3.0	F	5	1	1	Inhaled steroids	0
16	3.1	M	12	4	4	—	0
17	3.6	M	3	2	2	—	+
18	3.3	F	9	1	4	‡	+
19	4.3	F	6	2	3	Inhaled steroids†	+
20	4.8	F	3	3	3	—	+
21	3.1	F	10	3	3	Sodium cromoglycate	+
22	4.8	M	1	1	3	Inhaled steroids	+
23	4.6	M	8	2	2	—	0
24	3.2	F	2	0	0	—	0
Mean	3.5	M:F 17:7	4.6	2.04	2.9		

*Yes, +; No, 0.

†Started sodium cromoglycate or inhaled steroids during trial for intercurrent symptoms.

‡Started sodium cromoglycate or inhaled steroids at end of trial for intercurrent symptoms.

§Previously taken sodium cromoglycate or inhaled steroids but stopped as made no difference.

The outcome variables which were recorded for each episode included the need for hospital admission or oral corticosteroid treatment, day-time and night time symptom scores, additional bronchodilator usage and parents' assessment of the efficacy of the trial treatment.

Informed consent was obtained from a parent and the study had approval from the ethics committees of the three hospitals.

Paired *t* tests or a χ^2 test were used to compare the outcome of active and placebo treatments. Only completed pairs of treatments were used in the analysis.

Results

Twenty four children whose mean age was 3.5 years (table 1) completed 35 pairs of treatments. Thirteen recorded one pair each, the remainder completed two pairs. Their characteristics are shown in table 1. A further 11 children failed to

complete two episodes and were therefore excluded. Of these, six children did not experience two attacks of asthma during the two year trial period, despite their history (mean attack rate 2.2 episodes in the preceding three months). Another five subjects were withdrawn for social reasons: three because they moved out of the area and two whose parents were unable to cope with the protocol.

There was no measurable effect of active beclomethasone treatment on severe acute attacks, defined as those needing hospital admission or oral corticosteroid treatment (table 2). Numbers in each of these categories were rather small. Overall, significantly more parents considered beclomethasone to be helpful than reported benefit from the placebo inhaler ($p < 0.02$).

A direct comparison between the diary scores of all active and placebo treated episodes was

Table 2 Comparison of episodes after treatment with beclomethasone and placebo

	No of admissions	No who had steroids without admission	Parents' opinion		
			Helped	No help	Undetermined
Beclomethasone (n=35 episodes)	4	3	19	8	8
Placebo (n=35 episodes)	4	6	9	18	8
Significance of difference	NS	NS	$p < 0.02^*$		

*Analysis was of discordant pairs only (n=30 pairs).

Table 3 Comparison of mean scores during 18 pairs of active and placebo treated episodes in which neither a hospital admission nor treatment with oral steroids occurred

	Nights			Days		
	Duration of symptoms (days)	Mean score for first week	No of nights bronchodilators given during the night	Duration of symptoms (days)	Mean score for first week	No of days bronchodilators continued
Beclomethasone	6.1	0.92	3.38	6.11	0.82	7.0
Placebo	7.56	1.36	4.95	8.38	1.24	8.05
Difference (SE)	1.45 (1.36)	0.44 (0.18)	1.57 (0.92)	2.27 (1.3)	0.42 (0.16)	1.05 (0.92)
Significance of difference	$p < 0.5$	$p < 0.05$	$p < 0.5$	$p < 0.1$	$p < 0.02$	$p < 0.5$

not possible because of the need for oral corticosteroids or hospital admission. There were 18 intervention free pairs of episodes and the mean results obtained from the diary scores of these 36 episodes are shown in table 3. All mean scores were lower and bronchodilator usage less prolonged after beclomethasone treatment, although a significant difference, using a paired *t* test, was obtained only for the mean symptom score during the first week of the attack both for night ($p < 0.05$) and day ($p < 0.02$).

There was no effect of treatment order on symptoms scores. The interval between attacks and therefore treatments varied and no carry over effect was looked for.

Discussion

The short term use of high dose inhaled steroids for acute childhood asthma has not previously been reported, although the instruction to adults to 'double your inhaler dose at the first warning of an attack' seems recently to have become standard. Our results show a small reduction in symptoms during acute episodes of asthma thus treated. Several reasons for these rather inconclusive results should be considered.

Firstly, the dose of beclomethasone chosen and duration of treatment were purely empirical. A longer treatment period could have been more beneficial, although it is customary to use three days of oral corticosteroid treatment for acute severe childhood asthma, and even a single dose can be adequate.³ Secondly, the young age of the children being treated might have meant that in the presence of airflow obstruction they were unable to open the spacer valve adequately. From subsequent personal observations of spacer use in this age group, this seems probable in some cases. An appropriate valved spacer for preschool children has yet to be designed. The device that we used is representative of those which are commonly available. Thirdly, the patients included in this study were hospital based and it is a possibility that less severely affected children might have received greater benefit from our therapeutic approach. Certainly beclomethasone appeared to have little effect on the development of the more severe attacks, as it did not reduce hospital admission rate.

The most pertinent criticism levelled at marginal or negative clinical trials is that they were too small to produce a confident result. In this study the number of episodes available for detailed analysis was reduced from 70 to 36 because of therapeutic intervention during one or both of the paired treatment periods. If the power of this study is calculated by taking a 50% reduction in symptoms as a clinically important result,⁴ then 18 pairs of treatments were sufficient to show a difference at the 5% level for both day and night mean symptom scores. A smaller improvement or a higher degree of significance would require larger numbers. At least 45 pairs of treated episodes, however, would be required to show a 50% reduction in the duration of symptoms or of bronchodilator usage, at the 5% level. So the marginal outcome of this trial can in part be

explained by the relatively small number of episodes available for analysis. Detailed information about the natural history of acute episodic wheeze in this age group is not available. During the trial period there was a greater than anticipated reduction in the frequency of attacks and an increase in the variability in the response to viral infections in 3-4 year olds. This both reduced below our forecast the number of treated episodes and increased above our prediction the number needed to show a treatment difference. This age related change in symptomatology should be borne in mind in future clinical trials in preschool asthma.

The inadequacy of asthma diaries is recognised by all who attempt clinical trials in asthma. This trial was different from most as it was concerned with acute, and at times very severe symptoms only, in children who generally had prolonged symptom free periods. The scoring system would have perhaps more accurately described the situation if it had expanded the conventional 0-3 range used, to cater for the wide range of symptoms encountered. Also, it was impossible to make an accurate comparison of bronchodilator usage as a variety of dosages and methods of administration were used. The duration and not the amount of additional bronchodilator treatment was therefore used in the analysis and this may not have reflected the severity of the attack.

All except for one of the episodes was described as being associated with acute coryzal symptoms and in most cases fever was also present. This would support the view that acute asthma in this age group is precipitated by viral infections.⁵ Acute wheezing was a major feature in all the children but it is difficult to be certain how much of the symptomatology was additionally caused by bronchitis or post viral cough due to irritant receptor stimulation. The scoring system was not designed to differentiate between 'asthma' and 'non-asthma' symptoms that could coexist. The latter might not be expected to respond to steroid treatment and thus could mask the benefit to symptoms of asthma.

Despite many trials the efficacy of steroids in acute asthma of all ages remains controversial,⁶ although they are frequently used. Children under 18 months failed to show any benefit in one study but the subjects had been unwell for a mean of seven days before steroids were started.⁷ Early treatment has been advocated as being of greater benefit, although the trial on which this advice is based was not controlled.⁸ Storr *et al* also failed to show the benefit of a single dose of prednisolone in those under 2 years but showed some improvement in older children,³ as have others using short courses.^{9, 10} All the children in this study were over 18 months and there was no apparent age effect in the response to beclomethasone treatment. Other workers have failed to show any benefit either in children¹¹ or in adults.¹² As deaths from asthma have been attributed in part to delay in initiating steroid treatment¹³ one has to be careful that failure to show benefit is not simply the result of methodological problems rather than the result of a true lack of response.

Intermittent, high dose, inhaled steroid treatment offers a new therapeutic approach to the troublesome condition of severe, episodic asthma in young children. Should it be recommended in addition to bronchodilator treatment? Over half of the children in the present study were taking or had tried continuous treatment with either sodium cromoglycate or inhaled steroids and yet they continued to have troublesome frequent attacks. Also, there was no evidence that intermittent high dose beclomethasone was more effective in those taking continuous treatment. Currently available prophylactic treatment is therefore unlikely to be the solution to prevention of acute asthma in this age group. The alternative is the use of single doses or short courses of oral corticosteroids and it remains to be answered whether these are more effective than inhaled topical steroids, and whether frequent oral courses carry any risk of significant adrenal suppression. The result of this trial demonstrated some benefit despite possible methodological problems. The early use of inhaled steroids does not preclude later use of single or repeated doses of oral corticosteroids, if severe symptoms develop. Because of possible difficulties with the use of the spacer device in the younger children, assessment of the use of intermittent high dose, nebulised corticosteroids in a larger study might be the next step forward in tackling the difficult problem of treating

acute episodic wheeze in toddlers and preschool children.

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Food and drug reactions, wheezing, and eczema in preterm infants

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Abstract

Allergic reactions were investigated in 777 preterm infants who were randomly assigned to early diet and followed up to 18 months post term. Wheezing or asthma was common (incidence 23%); it was associated with neonatal ventilation, maternal smoking, and a family history of atopy and was unexpectedly reduced in babies born by caesarean section. Even in non-ventilated infants, the incidence of subsequent wheezing was 18%, rising to an estimated 44% (using logistic regression) when the foregoing risk factors (excluding ventilation) were present. Eczema occurred in 151 infants (19%) and was strongly associated with multiple pregnancy (30% incidence in twins or triplets). Reactions to cows' milk (incidence: 4.4% from detailed history; 0.8% confirmed by challenge), other foods (10%), and drugs (5%) were within the range reported in full term infants. Milk and food reactions were associated with multiple pregnancy (19%) and a family history of atopy. Reactions to drugs were least likely to occur in infants who had been ventilated and were on multiple medications in the neonatal period, suggesting that drug tolerance may have developed. We speculate that preterm infants may be a high risk group for asthma and eczema, which could imply an association between atopy and prematurity.

It is reasonable to suppose that preterm infants would be vulnerable to an increased incidence of later allergic reactions. They are commonly exposed to cows' milk antigens at a time when exclusion of whole antigenic proteins by the gut is poor,¹ and they are vulnerable to milk aspiration, a potent source of sensitisation.² They may also consume a greater load of food antigens for their size than mature infants, and have previously been shown to develop latent anaphylactic sensitisation to cows' milk.³ Moreover, premature babies are often heavily exposed to numerous drugs to which they might be sensitised. On the other hand, there is some evidence that preterm infants may be less liable to clinical sensitisation than more mature infants. For example, IgE production does not seem to occur before about 36 weeks' gestation.⁴ It is possible that increased antigen absorption from the gut may act as a suppressant to antibody production,⁵ a proposal supported by work in lower primates⁶ and by the finding of an increased population of suppressor T cells.⁷ Infants born very prematurely may also have less exposure to maternal anti-idiotypic anti-

bodies, which are thought to be important in the pathogenesis of childhood atopy.^{8,9} Despite these considerations, allergic reactions and the factors relating to them have been poorly documented in such infants. This paper reports data on allergic reactions in 777 infants born preterm who were followed up to 18 months of corrected age.

Subjects and methods

The subjects in this investigation are currently taking part in a five centre study designed to investigate the effects of early diet on later outcome in preterm infants. The overall objectives, study population, and design of this study have already been described.¹⁰ We report here the incidence of atopic or allergic disease in 777 infants who have been followed up until 18 months after the expected date of delivery.

Infants were recruited, with informed parental consent, in Cambridge, Ipswich, Kings Lynn, Norwich, and Sheffield. All infants weighed less than 1850 g at birth and were without major congenital abnormality. Mean (SD) birth weight was 1397 (298) g and mean gestation 31.0 (2.7) weeks. Details of atopic or allergic disease in the family were recorded while the infant was in the neonatal unit.

Infants in centres 1-3 were first seen for follow up at 9 (1) months' corrected age, and infants in all five centres were seen at 18 (1) months' corrected age. At the follow up examinations information was collected on eczema, wheezing (asthma), and food or drug sensitivities (see below). The history was supported as far as possible by clinical examination.

A single observer (RM) recorded the historical data in centres 1-4, achieving a follow up rate of over 95%. While other observers were involved at centre 5, in all cases they were blind to the infants' clinical course and management during the neonatal period.

Reactions to specific foods were classified as follows. (1) Cases with a convincing history of reaction(s) to a specific agent, resulting in its exclusion from the diet on professional advice. Such reactions were usually gastrointestinal or dermatological. (2) Cases where specific symptoms recurred on challenge conducted under controlled conditions. Reactions to drugs and household agents, mainly dermatological, were recorded similarly.

There has been much debate on the definition of asthma in infancy and childhood.¹¹ Godfrey suggests that the diagnosis should be based on intermittent cough or wheeze that can be reversed, largely or completely, by bronchodila-

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tors or steroids.¹² It is uncertain, however, whether recurrent untreated wheezing should be classified as asthma. We have used three categories: (a) 'recurrent wheezing', which refers to infants with at least three episodes of wheezing recorded by careful history, but where no drug treatment has been used; (b) 'moderate asthma': cough and wheeze requiring drug treatment either intermittently or continuously; and (c) 'severe asthma': cases requiring one or more hospital admissions for acute asthma. Other respiratory conditions characterised by noisy breathing, for example mucous rattling, were as far as possible excluded.

Atopic eczema was diagnosed from a clear history of itchy dermatitis with characteristic distribution, confirmed by clinical examination when active at the time of interview (60% of cases). Seborrhoeic dermatitis was not classified as eczema. Disease severity was classified as mild, requiring no treatment, moderate, requiring intermittent treatment (for example, steroid applications), and severe, reflecting the need for intensive treatment, usually after specialist referral.

Statistical analysis was by χ^2 test and multiple logistic regression analysis.

The study was approved by the local health authority ethics committee at each of the five hospitals and the Dunn Nutrition Unit.

Results

INCIDENCE OF ATOPIC OR ALLERGIC DISEASE

Table 1 shows the prevalence of atopic/allergic diseases in the 777 infants at 18 months' corrected age. Overall incidence of wheezing by this age was 22.5% (175/777) and of eczema 19.4% (151/777). Reactions to foods occurred in 10% (81/777) and to drugs in 5% (42/777). In all, 341 infants (44%) had had one or more manifestations of 'allergic' or atopic disease by 18 months of age.

All the atopic or allergic conditions investigated were highly correlated with one another.

Table 1 Incidence of wheezing or asthma, eczema, and food and drug reactions at 18 months' corrected age in 777 infants born preterm

	No of cases	Incidence (%)
Asthma or wheezing*:		
All cases	175	22.5
Intermittent wheezing	117	15.1
Moderate asthma	46	5.9
Severe asthma	12	1.5
Eczema*:		
All cases	151	19.4
Mild	48	6.2
Moderate	97	12.5
Severe	6	0.8
Food reactions:		
All cases† (one or more food)	81	10.4
Cows' milk		
Positive history	34	4.4
Confirmed by challenge	6	0.8
Egg	14	1.8
Other foods (including additives)	39	5.0
Drug reactions:		
All cases	42	5.4
Penicillin	25	3.2
One or more of the above conditions or reactions:	341	43.9

*For definitions see text.

†Reported reactions to foods where usually specific to one food; only six cases reacted to two foods and none to more than two.

Children with eczema were more than twice as likely to experience food reactions as children without eczema (27/151 (18%) compared with 54/626 (9%); $p < 0.001$), and significantly more likely to have asthma or wheezing (47/175 (27%) compared with 104/602 (17%); $p < 0.005$).

FACTORS ASSOCIATED WITH THE DEVELOPMENT OF ATOPIC OR ALLERGIC DISEASE

(a) Wheezing or asthma

Using logistic regression, factors examined for an independent association with wheezing or asthma (dependent variable) were: sex, birth weight, gestation, mode of delivery (vaginal or caesarean), days of mechanical ventilation (log transformed and +1 to avoid log 0), multiple pregnancy (twins or triplets), maternal steroids before delivery, small for gestational age (birth weight <10th centile), pregnancy induced hypertension (systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg), social class of parents, number of cigarettes smoked by mother and father, and number of first degree relatives with a history of allergic disease (asthma, eczema, hay fever, drug reactions, or proved food sensitivities). The only factors to emerge as independently related to wheezing or asthma were: duration of mechanical ventilation ($p < 0.001$), mode of delivery ($p < 0.01$), family history of allergy ($p < 0.01$), and maternal smoking ($p < 0.01$). The odds ratio of the infant developing wheezing or asthma in association with each factor is shown in table 2. The constant in the regression model shown was set as the 'best case' (lowest incidence of wheezing), which occurred in babies born by caesarean section from non-smoking mothers, who had no close family history of allergy and required no ventilation (relative risk 0.13:1; equivalent to an incidence of 11.5%). From the regression equation presented, the absolute risk of wheezing, based on the 'risk factors' shown, can be estimated from the constant and individual regression coefficients. Thus a non-ventilated infant with two atopic first degree relatives and who was delivered vaginally to a mother smoking 20 cigarettes per day, would have a relative risk of 0.8:1 (equivalent to 44% incidence). Table 3 shows raw data for the incidence and prevalence of wheezing or asthma broken down into categories for each of the significantly associated factors identified by the regression analysis. Notably 38% of infants ventilated for 10 days or more developed wheezing or asthma subsequently. No correlation at all was found between birth month and the development of asthma, in contrast to the findings in full term infants.^{13 14}

(b) Eczema

Using logistic regression (table 2), with independent variables as described above, the only factor found to be independently related to the incidence of eczema was multiple pregnancy (twins or triplets), which increased the relative odds by 2.1:1 ($p < 0.001$). Raw data (table 3) show an incidence of eczema of 30% in twins or triplets (39/130 cases) compared with 17% in singletons ($p < 0.005$).

Table 2 Relative odds of (a) wheezing or asthma or (b) eczema for each significantly associated factor identified by multiple logistic regression

Factor	Regression coefficient	SE	Relative odds
(a) Wheezing or asthma			
Vaginal delivery	0.50	0.18**	1.6:1
Duration of ventilation	0.34†	0.08***	1.6:1 for 3 days 2.0:1 for 7 days 2.6:1 for 15 days
Cigarettes smoked by mother/day	0.04	0.01**	1.2:1 for 5 cigarettes/day 1.5:1 for 10 cigarettes/day 2.3:1 for 20 cigarettes/day
No of first degree relatives with history of allergy‡	0.25	0.10*	1.3:1 for 1 relative 2.1:1 for 2 relatives
Constant (best case)§	-2.03		0.13:1
(b) Eczema			
Multiple birth	0.72	0.22***	2.0:1
Constant (best case)§	-1.56		0.21:1

* $p < 0.02$, ** $p < 0.01$, *** $p < 0.001$.†Regression coefficient derived using log transformed data: $\log_{10}$ (days of ventilation + 1).

‡Eczema, asthma, hay fever, or proved reactions to foods in first degree relatives.

§Constant set for lowest risk cases.

||Relative odds (odds ratio) for each factor are derived from the antilog of the regression coefficient and represent the odds relative to the corresponding lowest risk category.

Table 3 Raw data on overall incidence and prevalence at 18 months of wheezing, eczema, and food sensitivities, broken down by factors shown to be significantly related using logistic regression analysis (see table 2)

	Proportion of cases (% incidence)	p Value
Asthma or wheezing:		
(a) Ventilation		
None	72/410 (18)	
1-9 days	75/294 (26)	
>10 days	28/73 (38)	<0.0001
(b) Parental smoking		
No	107/545 (20)	
Yes	68/232 (29)	<0.005
(c) Caesarean section		
No	103/382 (27)	
Yes	72/395 (18)	<0.005
(d) Family history of allergy*		
(i) All cases		
No	104/577 (22)	
Yes	51/200 (26)	>0.05
(ii) Cases still symptomatic at 18 months		
No	82/577 (14)	
Yes	45/200 (23)	<0.01
Eczema:		
Multiple pregnancy		
No	112/647 (17)	
Yes	39/130 (30)	<0.005
Food sensitivities:		
Multiple pregnancy		
No	57/647 (9)	
Yes	24/130 (19)	<0.005
Family history of allergies		
No	51/577 (9)	
Yes	30/200 (15)	<0.02

*Family history was a significant factor for overall incidence of asthma when confounding factors were adjusted for - see table 2.

(c) Reactions to foods and drugs

Analysis of raw data showed reactions to foods were more common in twins or triplets ($p < 0.005$) and in infants who had a family history of allergy or atopy ($p < 0.02$) (table 3). These findings were confirmed by logistic regression analysis as above. Regression analysis also showed that drug reactions were appreciably more common in infants who were not ventilated (relative risk compared with ventilated infants, 2.5:1), despite lower drug exposure in the neonatal period in this group. There was a trend towards a lower incidence of reactions to penicillin by 18 months in those who had received penicillin in the neonatal period (2.3%; 11/473 cases) compared with those who had not (4.6%; 14/304).

The influence of early diet on later allergic

disease is an important area in its own right which is not considered in this paper and will be published separately. As described previously,¹⁰ infants were assigned in three centres to preterm formula and compared with donor breast milk (either as sole diets or as supplements to maternal milk). In the remaining two centres infants were assigned to a standard term formula and compared with a preterm formula (as sole diets or as supplements to maternal milk). For the purpose of interpreting results in this paper, however, our (unpublished) data show that while dietary effects on later allergy emerged in subgroup analyses, there was no overall effect of early diet on later allergic or atopic disease. Thus the conclusions presented here would not be altered if the proportions of infants on each diet were different to those in this study.

Discussion

In this study we have documented asthma or wheezing, eczema, and food or drug reactions at 18 months post term in nearly 800 infants born preterm. A number of important associations with these outcomes have been identified which may have broader significance for the aetiology of childhood atopy. As we suggest below, however, preterm infants may be, in certain respects, a special group in terms of the evolution of their atopic disease. The apparently high incidence of asthma and wheezing, which was intercorrelated with the incidence of eczema has led us to explore and develop the hypothesis that prematurity may be linked to atopic disease.

Our multicentre study was designed to investigate the effects of early diet (not reported here) on later outcome, including allergic reactions. The experimental design did not require full term control infants, as it was the difference between randomised groups of premature babies that was of importance. The principal purpose in this paper was to explore factors that relate to the development of allergic reactions within our population of preterm infants; again such analyses do not require full term control babies. It was also considered, however, that

our overall incidence figures for allergic reactions in infants born preterm should be presented here, though it must be emphasised that without using the same data collection procedure on infants born at term any comparison of our incidence figures with those published in term infants are of speculative significance. Nevertheless, such data have been collected in many studies using apparently similar diagnostic criteria to the ones used by us.

It is also reasonable to challenge the reliability of data on food reactions obtained mainly by clinical history. In this large multicentre study detailed immunological tests would have been impracticable and their value controversial. Our study is comparable with others,¹⁵⁻¹⁷ and has the advantage over several questionnaire based studies^{13 18-20} that a careful and consistent history was taken, in four centres, by one observer.

The incidence of wheezing or asthma appeared high. A diagnosis of intermittent wheezing was made at follow up after careful history by an experienced clinician, and moderate or severe 'asthma', requiring drug treatment, had usually been diagnosed by a paediatrician. The incidence of asthma in childhood has been reported to be between 0.1% and 19%, and even higher (up to 25%) if occasional wheezing is included.²¹ However, such high figures have not been reported for infants under 2 years of age. For example, data from the 1970 British cohort study using a questionnaire with less stringent diagnostic criteria than employed here,²² showed that by 5 years 21% of all children had had at least one wheezing episode; yet at 1 year the incidence was only 8.5%, and by 2 years, 11.5% (1318/11 465 cases). From published reports it seems unlikely that intermittent wheezing or frank asthma before 2 years would occur in more than 12% of infants born at term. Thus our 23% overall incidence at 18 months strongly suggests an excess in infants born preterm over that in the normal population.

It might be argued that the high rate of wheezing or asthma in infants born preterm is not an atopic manifestation but reflects lung damage after mechanical ventilation for early respiratory disease. Indeed, we found duration of ventilation was strongly associated with later wheezing or asthma, which occurred in nearly 40% of infants ventilated for 10 days or more. However, we suggest that ventilation was not the sole reason for this excess of cases. Firstly, wheezing or asthma was very common even in infants who received no mechanical ventilation at all, with an 18% overall incidence in this subgroup, rising to an estimated 44% in the 'worst case' for non-ventilated infants with other risk factors (see below). Secondly, wheeziness or asthma in this study was strongly associated with a family history of atopy, though only in the case of infants whose wheezing was still problematic at the time of the 18 month follow up. Finally, the incidence of wheezing or asthma was intercorrelated with that of eczema, generally regarded as an atopic disease. We have considered whether our incidence figure for eczema of 19.4% should be regarded as high. Kjellman¹⁸ and Croner *et al*,¹⁹ who collected their data in a similar way to ours, reported inci-

dence rates of only 7.6% and 5.7% in prospective studies of European (Swedish) term infants. The incidence figures for eczema reported in this country have, however, risen in recent years, from 5% in the 1946 national birth cohort to 12% in the 1970 cohort,²³ though these figures represent incidence up to 6 years of age and cannot be compared with our 18 month incidence. More recent data (1981) from New Zealand, however, showed an incidence of 12% in 2 year old infants with no atopic family history (compared with 18% in our study).²⁴ Interestingly, though, this study demonstrated that in the subgroup of children with a positive atopic family history, the incidence of eczema (24%) was similar to ours (25%). Further study, comparing preterm and term infants using the same data collection procedure, would be needed to examine the possibility raised here, that preterm infants are a high risk group for eczema.

The hypothesis presented that wheezing or asthma in preterm infants may often have an atopic basis requires future investigation. Indeed, the arguments presented above have some inconsistencies: for example, while we show that eczema and wheezing are intercorrelated, these disease states are also to some extent independent as evidenced by a difference in the pattern of associated factors (table 2). Nevertheless, an atopic aetiology for wheezing in preterm infants is further supported by the data of others. Bertrand *et al* showed that preterm infants, whether ventilated or not, are subject to airways hyper-reactivity.²⁵ The tendency to wheeze after mechanical ventilation, observed also in smaller case controlled studies by others,^{25 26} could be interpreted as an exacerbating effect of ventilation in infants predisposed, perhaps genetically, to atopic respiratory disease. Furthermore, the association between ventilation and later wheezing could imply that atopic infants are the ones most likely to develop severe early respiratory disease and hence have an increased requirement for ventilation.

Bertrand *et al* observed that not only do preterm infants have increased 'bronchial hyper-reactivity' but so also do their mothers,²⁵ raising the intriguing possibility that hyper-reactivity of the smooth muscle in the bronchi could be associated with hyper-reactivity of that of the uterus, as a potential mechanism for preterm labour. This concept is debated however; Chan *et al* were unable to substantiate Bertrand's hypothesis.²⁷ We did not perform bronchial hyper-reactivity tests and the number of mothers with frank asthma was too small for detailed analysis. Nevertheless, our surprising observation that preterm infants delivered by caesarean section were less likely to develop later wheeziness could be explained if it is argued that the great majority of such babies were delivered interventively, largely for complications arising in pregnancy, and therefore they constituted a different group, in terms of familial atopy risk, to those whose mothers went into spontaneous preterm labour.

In contrast to the high incidence of wheezing in preterm infants, the incidence of cows' milk

reactions (4.4% based on clinical history; 0.8% confirmed by objective challenge) and of reactions to foods in general (10%), was well within the range reported for normal children, in whom incidence of food allergies has been claimed to be as high as 20–40%.^{17 19 28 29}

Few investigators have published incidence figures for drug reactions in early childhood, but Croner's value of 7.3% (116 cases in 1701 infants) was similar to our figure of 5.4% (42/779).¹⁹ Yet, in view of the very high antibiotic and drug usage in low birthweight infants a high rate of subsequent drug reactions might be predicted. On the contrary, the 2.5 fold greater risk of drug reactions in well, non-ventilated compared with sick, ventilated infants (the latter receiving more drugs), together with the trend towards a lower rate of penicillin reactions in infants who had received penicillin in the neonatal period, suggests that preterm infants may develop tolerance to drugs.

Aetiological factors for atopic disease and allergic reactions in preterm infants may not be the same as those factors proposed for babies born at term. For instance, there was no suggestion that any of the outcome responses in this study had a seasonal incidence, as has been found with atopy in full term infants.^{13 14} An unexpected independent association, which demands further exploration, and not described in full term infants, is the raised incidence of eczema and food sensitivity in twins and triplets: indeed for both eczema and food sensitivities multiple birth emerged as the most strongly associated factor. Various studies have examined the concordance of eczema in monozygotic and dizygotic twins^{30 31}; but if twinning per se is associated with eczema, we may question the validity of such concordance studies regarding the genetic risk for eczema in the population. Maternal smoking, as in term pregnancies,³² emerged as a strongly associated independent factor for wheezing or asthma in the infant. The association between atopic disease or food sensitivities in the preterm baby and a family history of atopy suggests that genetic factors were of major aetiological significance.

Perhaps the most important questions raised by our data, and requiring further exploration are: whether wheezing and eczema do indeed have an increased incidence in preterm infants; whether or not wheezing in such infants should be regarded as having principally an atopic basis; whether prematurity is linked to atopic disease; and finally, whether atopy has aetiological importance in preterm labour.

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Neurotoxicity in lymphoblastic leukaemia: comparison of oral and intramuscular methotrexate and two doses of radiation

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Abstract

Serial cranial computed tomograms were carried out in 136 children with acute lymphoblastic leukaemia who were receiving 24 Gy or 18 Gy of cranial irradiation and continuing treatment with doses of methotrexate given weekly orally or intramuscularly. The findings were correlated with treatment variables, the development of fits, and the intelligence quotient (IQ). Reversible brain shrinkage, attributed to treatment with steroids, was found on 87 of 114 initial scans (76%); 14 showed changes in white matter during treatment (10%), and calcification was found in 13 either during or after treatment (10%). Eight children (6%) had fits, and in six of the eight there were changes in white matter or calcification on the scans. Comparison of the two radiotherapy dosages showed no difference in the incidence of abnormalities seen on computed tomography, fits, or serial IQ measurements, but children receiving intramuscular methotrexate had a higher incidence of calcification and a lower mean IQ at one year than those who received the drug orally, although this difference was not apparent later. Younger children were more likely to develop changes on computed tomograms and fits, and to have low IQs on completion of treatment, with changes most apparent in those less than 2 years of age. There were highly significant correlations between abnormalities on computed tomography, fits, and IQ. These findings confirm the neurological vulnerability of younger children with acute lymphoblastic leukaemia, show an association between abnormalities on computed tomography and intellectual deficit, and suggest that methotrexate is more toxic when given intramuscularly than orally. They provide no evidence that 18 Gy of cranial irradiation is less toxic than 24 Gy, and indicate the need for alternative treatment regimens.

Now that large numbers of children with acute lymphoblastic leukaemia are surviving for long periods, and many are cured, it has become apparent that an appreciable minority develop late effects of treatment.¹ These include impaired growth and endocrine problems,¹ and a range of neuropsychological disorders varying from subtle learning difficulties² and abnormalities on computed tomography³ to overt neurological deterioration, dementia, and convulsions.⁴ Though such complications are, not surprisingly, more common among children who have received more than one course of treatment,¹

their occurrence has led to reappraisal of certain aspects of treatment, most notably that directed to the central nervous system (so called 'central nervous system prophylaxis'). The most commonly used central nervous system treatment has been a course of cranial irradiation in a dose of 24 Gy, and intrathecal injections of methotrexate. At the same time a desire to decrease the rate of bone marrow relapse has led to investigation of drug dosage and timing, particularly during continuing (maintenance) treatment. Our concern about the variability of absorption of methotrexate led us to compare the oral and intramuscular routes of administration during continuing treatment of acute lymphoblastic leukaemia. We report here the results of investigations in a group of children with acute lymphoblastic leukaemia who received either 24 Gy or 18 Gy of central nervous system irradiation, and methotrexate given either orally or intramuscularly.

Patients and methods

Between 1979 and 1982, all children with non-T cell acute lymphoblastic leukaemia referred to this hospital were treated with a standard induction protocol comprising daunorubicin, vincristine, prednisolone and crisantaspase (L-asparaginase) and then, after treatment of the central nervous system was completed, continuing treatment with 6-mercaptopurine daily for two weeks in three, prednisolone and vincristine every six weeks, and methotrexate in a single weekly dose of 20 mg/m². Children were randomly allocated to receive the methotrexate by mouth or as a single weekly intramuscular injection. This phase of treatment was continued for a total of 96 weeks. All children received treatment of the central nervous system which comprised methotrexate given intrathecally for six doses, and a course of cranial irradiation. Cranial irradiation was given for the first part of the trial in a dose of 24 Gy in 15 fractions over three weeks and, in January 1981, was reduced to 18 Gy in 10 fractions given over two weeks. Thus the allocation of the dose of radiotherapy, unlike the route of administration of the methotrexate, was not random.

Children who were under 2 years of age at the time of diagnosis received regular intrathecal injections of methotrexate every six weeks until their second birthday, when radiotherapy was given in a dose of 18 Gy in 10 fractions over two weeks. The details of this protocol have been published,⁵ and the design is shown in the figure. It was planned that children on this protocol should receive serial computed tomo-

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'PLOT' protocol for non-T, non-B acute lymphoblastic leukaemia. Numbers refer to doses of drug in mg/m²/surface area except for crisantaspase (L-asparaginase), which is in units/m²/surface area.

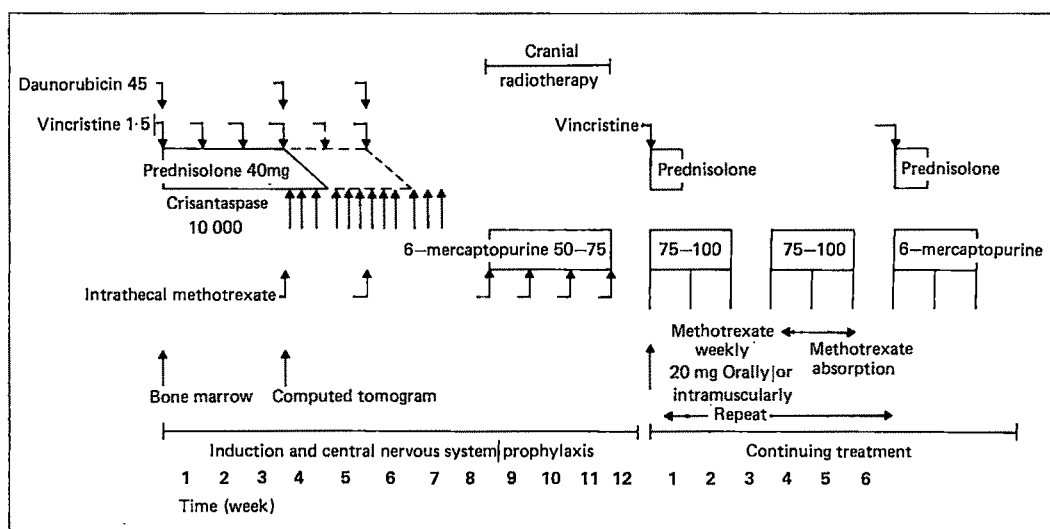


Table 1 Numbers of patients and investigations

Age at diagnosis (years)	Total patients*	Route of methotrexate		Cranial irradiation		IQ assessment	
		Oral	Intramuscular	24 Gy	18 Gy	Serial	Late only
<2	18 (8)	13 (6)	5 (2)	Deferred		0	11
2-5	65 (39)	31 (22)	34 (17)	25 (16)	40 (23)	27	23
5-10	44 (23)	24 (11)	20 (12)	19 (9)	25 (14)	28	10
10+	9 (4)	3 (1)	6 (3)	4 (1)	5 (3)	5	1
Total	136	71	65	48	70	60	45

*Number of boys in parentheses.

graphy, psychological assessment, and neurological examination. The numbers of children in whom each of these investigations was carried out is shown in table 1.

Whenever possible all patients had a computed tomogram within a week of diagnosis and again at one year, two years, and (when possible) between four and five years from diagnosis. Routine scans were performed with sedation where necessary using an EMI 1010 head scanner or Toshiba-60 without intravenous contrast. The scans were assessed by two observers (TCSC and BK) who had no knowledge of the clinical variables. A grading system was used to determine the degree of brain shrinkage (ventricular dilatation or wide superficial subarachnoid spaces) changes in white matter, or calcification; the presence of any abnormality was noted.

The numerical grading system was devised by comparison with normal control scans. An attempt was thus made to determine whether any of the changes noted were progressive. Progression was defined as an increase in the numerical grading score seen on two or more consecutive scans. The serial scans for each patient were assessed together.

Patients had psychological assessments before radiotherapy and at one and two years (and later) follow up when possible. Assessment included measures of general intelligence (IQ) using the revised Wechsler intelligence scale for children for those over the age of 6 years.⁶ The McCarthy scales of children's abilities,⁷ and the British ability scales,⁸ were used for children under the age of 6 years. The attainments of children of school age were assessed with the British ability scales. Assessment of all children

was not possible for logistic reasons, and some children, together with those aged less than 2 at diagnosis, had a single IQ test on completion of treatment.

The patients were seen by a paediatric neurologist within six months of completion of treatment, or sooner in the event of overt neurological problems. A history was taken of the pregnancy and delivery, birth weight, developmental milestones, and of previous illnesses. Details of the family history were recorded. A history was also taken of any symptoms during the treatment: weakness, unsteadiness, headaches, or visual disturbance. Information about any fits, their nature and frequency, were also recorded.

The child was given a neurological examination and a record was made of clumsiness (dyspraxia) and joint mobility. Head circumference and visual acuity were recorded and a note was made of whether the child was left or right handed.

The overall design of the trial, and the pharmacokinetics of methotrexate, have been reported in detail elsewhere. At the time of the first report there was no significant difference in event free survival between children receiving methotrexate orally or intramuscularly. The data were analysed again in December 1988 (minimum follow up for all patients of six years) and there remains no difference in survival between the children in the two treatment groups. Children who relapsed were withdrawn from the study, but results of investigations carried out before relapse are included.

The associations between variables (such as abnormalities on computed tomograms, fits, and treatment regimens) were tested by χ^2

analysis. Because of the association between abnormalities and age, comparisons of treatments were adjusted for age by calculating the difference between observed and expected findings and its variance, and summing over the age group.⁹ Any differences in mean IQ between treatment groups at two years and between those with and without abnormalities on computed tomography were assessed by Student's *t* test.

A χ^2 test for trend was used to see if there were any trends towards more abnormalities at younger ages, and one way analysis of variance was used to see if there was any association between IQ two years after diagnosis and age.

The number of patients who had IQ tests both at diagnosis and later was quite small, so to look for any effect of treatment on serial IQ, the Mann-Whitney test was used to compare the apparent percentage increases in IQ from diagnosis to one year, and from diagnosis to two years, between treatment groups. This allows for the non-normal distribution of the percentage increases. Most analyses were performed using the statistical software package BMDP.¹⁰

Permission for the study and accompanying investigations was given by the joint ethics committee of the Hospital for Sick Children and Institute of Child Health.

Results

One hundred and sixty four children were entered into the study, of whom 158 achieved remission. Three children with Down's syndrome and one whose mother had Down's syndrome were excluded from the study, together with one infant (the only patient in the series) in whom central nervous system disease was present at the time of first lumbar puncture. Seventeen patients were not available for computed tomography either because the parents did not consent to the investigation or they lived too far away, and thus this report concerns the remaining 136 (table 1). The patients are divided by age: under 2 years, 2 to 5, 5 to 10, and over 10 years. The numbers of investigations performed in each group are given.

CHILDREN UNDER 2 YEARS

Eighteen children were under 2 years old at the time of diagnosis, five of whom received intramuscular and 13 oral methotrexate. Fifteen of 17 scans carried out on children within the first three weeks of presentation showed brain shrinkage, but this was not progressive in any of the 14 who had follow up scans. Change in

white matter was found in four of the 14 children scanned again at one year or subsequently, and calcification in three of 14. Changes in white matter detected at two years were not detected on later follow up in three children, but calcification was equally prominent in two of the three children with previous changes who were scanned again at five years. The full scale IQ obtained after completion of treatment in 11 children ranged from 61 to 124 (mean 90), but only one child in the series had an IQ of more than 100, and only three had IQs between 90 and 100. One child, with a coexistent left sided arachnoid cyst on computed tomography, had had fits before the onset of treatment, and three others had fits during or after treatment. Of the 11 children who had neurological examinations on completion of treatment, one showed some clumsiness, three had exaggerated knee reflexes, and five had hypermobility of their joints.

CHILDREN AGED 2 TO 5 (table 2)

There were 65 children in this group; 51 had some brain shrinkage on at least one scan, 43 on the first. Two had progressive brain shrinkage. Change in white matter during the first two years was detected in seven children, but did not progress on subsequent scans. At longer follow up, change in white matter was only detectable in one child. Calcification, however, was noted in five children during the first two years, and a further four at four to five years' follow up. Full scale IQ gave a mean value of 109 at one year, 107.6 at two years, and 118 at four to five years. Four of the children in this age group had had one or more fits associated with fever before the start of treatment; none of these developed fits during or after treatment. Five additional children had fits during or after treatment, four of whom were receiving methotrexate intramuscularly. Neurological examination of 46 children showed that 14 were clumsy, 11 had exaggerated knee reflexes, and 26 had hyperextensible joints.

CHILDREN OVER 5 YEARS OF AGE (table 3)

As there were only nine children in the study who were over 10 years of age at the time of diagnosis, the findings of those who were over 5 and those who were over 10 are shown in table 3. There were 44 children below 10, and nine over 10. Brain shrinkage was noted in 29 of 43 at the beginning of treatment but did not progress in any of them. Change in white matter was detected in two during the first two years

Table 2 Results of computed tomography and IQ testing in children aged 2-5 years

	Before radiotherapy	1 year	2 years	4-5 years	Abnormal at any time	Progressive abnormality
Computed tomography:						
Total No of scans	54	59	55	40		
No that showed brain shrinkage	43	17	9	1	51	2
No that showed changes in white matter	0	5	5	1	8	0
No that showed calcification	0	1	5	7	9	0
IQ testing:						
Total No tested	28	26	48	12		
Mean score (range)	108.7 (82-150)	109.0 (84-142)	107.6 (75-147)	118.8 (96-147)		

Table 3 Results of computed tomography and IQ testing in children aged over 5 years

	Before radiotherapy	1 year	2 years	4-5 years	Abnormal at any time	Progressive abnormality
Computed tomography:						
Total No of scans	43	47	41	24		
No that showed brain shrinkage	29	19	17	2	36	0
No that showed changes in white matter	0	2	2	0	2	0
No that showed calcification	0	0	1	1	1	0
IQ testing:						
Total No tested	38	33	41	12		
Mean score (range)	113.9 (84-144)	114.8 (81-138)	112.9 (61-142)	115.8 (95-136)		

but not later in any patient. Calcification was found in one child, but no child had progressive calcification or change in white matter. Calcification and change in white matter were only seen in children who received methotrexate intramuscularly. The mean IQ at diagnosis was 113.9, at two years 112.9, and at long term follow up 115.8. Thirteen of 51 children examined on completion of treatment were clumsy, 16 had exaggerated knee reflexes, and 10 had hyperextensible joints. Three children in this age group had had one or more fits before treatment in association with fever, but no child developed convulsions during or after treatment, and no other child in this age group subsequently developed convulsions.

OVERT NEUROLOGICAL ABNORMALITIES

Eight children had histories of one or more fits before treatment. In seven (all aged under 6 at the time of diagnosis) the fits seemed to have occurred in association with fever. The eighth child is discussed below. None of these children seemed susceptible to fits during treatment. Eight additional children developed fits during or after treatment of whom two had no abnormalities on computed tomography. The other six developed convulsions during or after treatment, and the scan showed change in white matter or calcification. In three of these there was obvious simultaneous neurological deterioration. Further details on these children are given in table 4. All were aged under 5 at the time of diagnosis but only one was under 2; five were receiving methotrexate intramuscularly. One child (case 6) developed an acute encephalopathy that was presumed to be viral, and at necropsy measles encephalitis was found. In no other child was a viral cause found for neurological problems.

Two children (cases 4 and 5) developed progressive convulsions with calcification and changes in white matter. Both were receiving methotrexate intramuscularly, and both subsequently relapsed, one receiving further methotrexate. At subsequent follow up there was neurological deterioration and persisting fits. Both were thought clinically to have methotrexate leucoencephalopathy but unfortunately permission for necropsy was not obtained for either. Three children survived, one (case 2), the only one in the series who received methotrexate orally, is well with prominent calcification on scan; his fits have stopped but he has a full scale IQ of 79 and requires remedial help at school. Case 1, who was 14 months old at the time of diagnosis and received methotrexate intramuscularly and long term methotrexate intrathecally, is also well but has an IQ of 61 and severe learning problems. Case 2 has had severe grand mal convulsions that started after completion of treatment, and calcification was first noted on her scan five years after diagnosis. She has appreciable learning problems, an IQ of 79, and became pubertal at the age of 8.2 years. One additional infant (case 7 who was described previously) was found to have an arachnoid cyst; he subsequently relapsed and died. The two year scan of one further child (not mentioned in the table) is suggestive of an infarct, but the child is well and free of symptoms, has no learning problems, and an IQ of 124.

ANALYSIS OF IQ

At the time of diagnosis the mean IQ of the whole sample was within the normal high average range of intelligence and the distribution of values was normal. Table 5 shows the mean (SD) IQs of the two radiotherapy and methotrexate groups for those patients who had tests

Table 4 Clinical details of children with fits and abnormal computed tomograms

Case No	Age at diagnosis (years)	Route by which methotrexate given	Radiotherapy	Findings on computed tomography	Complications
1	1.1	Intramuscular	Deferred	Atrophy, white matter change, calcification	Fits; IQ 61
2	2.0	Oral	20 Gy	Persistent calcification; change in white matter after one year of treatment	Fits; IQ 79
3	2.0	Intramuscular	18 Gy	Late (4 years) calcification	Grand mal fits; an episode of hemiplegia; early puberty; IQ 75
4	4.0	Intramuscular	24 Gy	Atrophy, white matter change	Persistent fits; progressive abnormality on computed tomography; died in relapse
5	3.3	Intramuscular	24 Gy	Atrophy, white matter change, calcification	Relapse; further methotrexate given; died
6	3.0	Intramuscular	24 Gy	Calcification, white matter change	Progressive central nervous system deterioration and fits; measles
7	1.0	Oral	Deferred	Subarachnoid cyst left temporal region	Fits before treatment; relapse at two years

Table 5 Average IQ at diagnosis and during follow up according to dose of radiotherapy and route by which methotrexate given

	At diagnosis		At 1 year		At 2 years	
	No tested	Mean (SD) IQ	No tested	Mean (SD) IQ	No tested	Mean (SD) IQ
Radiotherapy: 24 Gy	21	116.0 (12.7)	21	115.9 (13.6)	21	115.7 (15.4)
Radiotherapy: 18 Gy	33	111.5 (16.4)	33	111.2 (15.9)	33	113.6 (15.2)
Methotrexate: oral	26	115.2 (15.5)	26	117.2 (14.3)	26	118.5 (16.2)
Methotrexate: intramuscular	28	111.4 (14.8)	28	109.1 (14.9)	28	110.6 (13.4)

at the time of diagnosis, and at one and two years.

Whereas there was an apparent slight increase in the mean IQs of children receiving methotrexate orally, those of children receiving methotrexate intramuscularly showed an apparent decrease. Analysis of variance showed no significant difference between these results. Estimation of the percentage increase in IQ from presentation to one year using the Mann-Whitney (non-parametric) test, showed a significant difference between the children receiving methotrexate orally and intramuscularly, but this difference was not sustained when the values at presentation and at two years were compared. There were no significant differences between the two radiotherapy groups.

RISK FACTORS FOR DEVELOPMENT OF ABNORMALITIES

There was no association between age at the time of diagnosis and the appearance of brain shrinkage on computed tomography, but younger children were significantly more likely to develop changes in white matter ($p < 0.025$), calcification, ($p < 0.025$), fits ($p < 0.01$), and hyperextensible joints ($p < 0.01$) than older children; they were not, however, more likely to be clumsy. The IQ on completion of treatment was significantly lower ($p = 0.0006$) in the under 2 year olds, and a regression analysis of IQ and age showed a significant correlation ($p = 0.01$).

There was no association between any of the findings on computed tomography or any

neurological abnormality, and the sex of the child.

Children who received 24 Gy of irradiation were at no more risk of abnormalities visible on scans than those receiving 18 Gy (table 6). Table 6 also shows the influence of route of administration of the methotrexate. Although more children who received methotrexate intramuscularly developed change in white matter (9/65 compared with 5/71), this difference was not significant, nor was the difference in the incidence of fits, but calcification was found more often in those receiving methotrexate intramuscularly ($p = 0.03$). This significance disappeared when allowance was made for age.

INTER-RELATIONSHIP OF ABNORMALITIES (table 7)

There was no relationship between the presence of brain shrinkage on computed tomography and the development of fits or the assessment of IQ. There seemed to be an association between clumsiness on neurological follow up examination and the presence of atrophy on the final follow up scan. Children with change in white matter or calcification seen on the scan were significantly more likely to have fits, but there was no association between these findings and any other neurological symptoms. There was a highly significant correlation between the occurrence of fits during or after treatment and the IQ, and between these findings and changes on computed tomography.

PROBLEMS OF GROWTH AND DEVELOPMENT

Prospective assessment of endocrine function

Table 6 Results according to dose of radiotherapy and route of administration of methotrexate

	Dose of radiotherapy*		Route of administration of methotrexate	
	24 Gy	18 Gy	Oral	Intramuscular
Total No	48	70	71	65
Abnormalities on computed tomography:				
No that showed brain shrinkage	33	54	53	49
No that showed changes in white matter	3	7	5	9
No that showed calcification	3	7	3	10
No that developed fits	4	1	2	6
IQ at two years:				
No tested	31	59	52	48
Mean IQ	110	109.4	109.1	105.5

*Children aged <2 years were excluded.

Table 7 Inter-relationship of abnormalities

	Abnormalities on computed tomography			Fits
	Brain shrinkage	Changes in white matter	Calcification	
Fits	NS	0.0001	<0.0005	Not applicable
Low IQ	NS	0.03	0.0001	<0.0005
Headache	NS	NS	NS	NS
Clumsiness	0.05	NS	NS	NS
Hyperextensibility of joints	NS	NS	NS	NS
Exaggerated reflexes	NS	NS	NS	NS

was not a part of this study. The youngest children have now reached the age of 9–10 years, and precocious or early puberty has been noted in nine girls and premature adrenarche in one boy. There is no association between the dose of cranial irradiation or the route of administration of methotrexate, and the onset of early puberty. Assessment of growth hormone was not undertaken, but one additional boy has declined further investigation and has clinical growth hormone deficiency.

Discussion

A wide range of neuropsychological problems occur in children who are treated for acute lymphoblastic leukaemia. These include learning difficulties and low or declining IQ scores,^{2–11} usually more pronounced in younger children,¹² and even neurological deterioration, dementia, and necrotising leucoencephalopathy.⁴ Though leucoencephalopathy has most frequently been reported in children treated for one or more episodes of leukaemia of the central nervous system, usually with radiation and prolonged intrathecal chemotherapy,¹³ it has also been described in children in first remission who have received methotrexate intrathecally together with cranial irradiation, and subsequent methotrexate given intravenously.^{14–15} Computed tomography of the brain in methotrexate radiation encephalopathy has been well described, and abnormalities include ventricular and subarachnoid dilatation, low attenuation of white matter, and intracerebral calcification.¹⁶ Similar changes may be found, however, in children without symptoms who are treated for acute lymphoblastic leukaemia, although the incidence of such change varies and may well be associated with the type of central nervous system treatment. It has been reported that computed tomographic changes such as calcification and cortical atrophy show strong correlation with the extent of intellectual impairment.¹⁷ Seizures, though a feature of methotrexate encephalopathy, also occur in up to 10% of children with acute lymphoblastic leukaemia and may be more common in those receiving the drug intrathecally and intravenously than in those receiving cranial irradiation and short term methotrexate intrathecally.¹⁸

Clearly there is no single cause of these problems, and it has even been argued that many, if not all of the learning problems may be attributed to the effects of leukaemia itself or those of chronic illness, rather than to treatment directed at the central nervous system.¹⁹ Prospective psychometric studies are hampered by the young age of many of the patients and the high attrition rate of the disease. A recent meta-analysis of most papers published on the subject, however, has concluded that most, if not all, of the problems are the result of the treatment rather than the disease.²⁰

The three main therapeutic components predisposing to central nervous system damage in children treated for acute lymphoblastic leukaemia have been identified as cranial irradiation, methotrexate given intravenously, and methotrexate given intrathecally.⁴ Analysis of

their individual contribution to damage is difficult, because all three treatments are frequently given in conjunction.

These concerns have led to reappraisal and modification of treatment directed at the central nervous system but such changes must be tempered by the realisation that all children with acute lymphoblastic leukaemia are at some risk of central nervous system relapse, and that the outcome after overt central nervous system leukaemia is poor.²¹

Regular intrathecal chemotherapy without cranial irradiation may be adequate for some patients,²² and there is some retrospective evidence that it is less damaging,^{23–24} but patients receiving regular methotrexate intrathecally and intravenously have been reported as showing more abnormalities on computed tomography and similar IQ scores when compared with those receiving short term treatment intrathecally together with cranial irradiation.^{25–26}

Our decision to reduce the dose of cranial irradiation during the study was prompted by these concerns and by the report from the American Children's Cancer Study Group that a dose of 18 Gy was as effective as 24 Gy in treatment of the central nervous system,²⁷ and we hoped that it would prove less toxic. Similarly, by deferring irradiation in children under 2 years old, we hoped to reduce the problems in young children. The randomised comparison of methotrexate given orally and intramuscularly was undertaken with knowledge of the variable concentrations obtained after oral treatment,²⁸ confirmed by us during this work,²⁹ and in the hope that methotrexate given intramuscularly would decrease the bone marrow and testicular relapse rate. The work reported here was planned prospectively to monitor any potential toxicity. We had calculated that the dose of methotrexate of 20 mg/m² needed for intramuscular use was much lower than that of 40–60 mg that was reported to cause neurological dysfunction.^{14–15}

Our results, however, show that there was no difference in the incidence of abnormalities on computed tomography, fits, or changes in IQs, in the two groups of children who received either 18 or 24 Gy. Moreover, as we have previously reported, the incidence of precocious puberty, and thus presumably pituitary-hypothalamic dysfunction, remains similar.³⁰ Thus we have no evidence to suggest that the lower dose of irradiation is less toxic.

By contrast, we found some evidence that methotrexate given intramuscularly was more toxic than when given orally; more children receiving the drug intramuscularly developed attenuation of white matter and fits during or after treatment in association with abnormalities on scans. These results were not significant, but they are suggestive, particularly in view of the additional finding of increased calcification in the group receiving the drug intramuscularly. There was also some evidence that IQ measurements declined in children receiving methotrexate intramuscularly, although this finding was not sustained on longer follow up. Four of the five children who developed repeated fits in

association with abnormalities on their scans were receiving methotrexate intramuscularly. Though all three of the five who survived have serious learning problems, none has the focal neurological abnormality or continued deterioration described in gross encephalopathy associated with higher dose methotrexate given intravenously.

Our analysis of the risk factors for neuropsychological damage in this study confirms once again the vulnerability of young children, but not that of girls that has been reported by others.³¹ In retrospect, our decision to defer irradiation in those under 2 years old possibly contributed to these results, as these children received prolonged intrathecal chemotherapy as well as irradiation. New regimens for this age group are clearly indicated.

Our results also show that younger children are also more likely to develop abnormalities on computed tomography. It is difficult to compare our incidence of abnormalities with those reported by others because the details of treatment vary; for example, one of the highest rates of abnormalities has been reported in children receiving cranial irradiation and monthly intrathecal chemotherapy.³ The high incidence of brain shrinkage we noted on the initial scans reflected treatment with steroids and was presumably reversible damage. The incidence of long term atrophy was much lower. We noted, like others,²⁵ that the appearance of attenuation of white matter did not necessarily persist in follow up scans; this abnormality would have been more effectively assessed by nuclear magnetic resonance.³²

Calcification, in contrast to change in white matter, may not develop for some years after the start of treatment,³³ and several of our patients showed this late change. There was a highly significant correlation between the IQ and the presence of calcification or attenuation of white matter on scan, a relationship also noted in a group of 23 children in a previous study.¹⁷ We have thus shown that in a group of children receiving treatment for acute lymphoblastic leukaemia, abnormalities of computed tomography, fits, and a low IQ all tend to occur in association; that younger children are more vulnerable to all of these problems; and that vulnerability may be exacerbated by the use of moderate intramuscular doses of methotrexate. Neuropsychological problems were not ameliorated by the reduction of cranial irradiation from 24 to 18 Gy, or by deferring radiotherapy in the younger children. These results highlight the need for effective alternative treatment of the central nervous system, particularly in the younger child, but attempts to evaluate such alternatives should be accompanied by prospective neuropsychological assessment.

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The sexually abused battered child

C J Hobbs, J M Wynne

Abstract

A total of 130 children were identified in whom both evidence of sexual abuse and non-accidental, non-genital physical injuries (bruises, fractures, scratches, burns and scalds, including failure to thrive) were found. There were 77 girls and 53 boys with mean ages 5.7 and 6.8 years respectively and the peak age between the second and seventh birthdays; this reflects previous reports indicating that physical and sexual abuse predominantly involves young children.

Patterns of injury that suggested sexually motivated assault included bruises, scratches, and burns around the lower trunk and genitalia, thighs, buttocks, and upper legs including knees. Pinch and grip marks were found where the child was held. The sexual abuse often involved attempted or achieved penetration of mouth, vagina, or anus, and physical signs were seen relatively more often than in sexually abused children as a whole. Four children died and sexual aggression and child death in the domestic setting may be linked. One in six of 769 physically abused children (16.9%) and one in seven of 949 sexually abused children (13.6%) have suffered both forms of abuse.

Non-accidental injury in the form of bruises, bites, burns, lacerations, fractures, and head injuries as well as other characteristic patterns of injury such as subdural haematoma and retinal haemorrhage, has been increasingly recognised over the past 30 years since first reaching professional attention. In the original descriptions of battered children no mention was made of findings that would indicate that there had also been sexual abuse.^{1,2} With the recent awareness of child sexual abuse on both sides of the Atlantic has come an appreciation that physical and sexual abuse can coexist.³

One of the first attempts to examine a series of sexually abused children in the United Kingdom found that in 15% of sexually abused children there was evidence of physical injury and in 7% there was a history of previous injury.⁴ In an earlier publication we described our finding that one in 10 of 337 sexually abused children had presented to us after physical abuse.⁵ Since then our experience of both physical and sexual abuse has increased and the presence of an overlap between these forms of abuse has become clear. We therefore decided to review our experience over the four years in which increasing numbers of sexually abused children have come to our attention.

Children studied

In the four years 1985-8 inclusive we diagnosed physical abuse in 769 children and sexual abuse in 949 children. These totals included 130 children in whom both physical and sexual abuse was diagnosed. Details of the number of children in each year are to be found in table 1. These 1588 children represented 55% of 2883 children referred with suspected child abuse or neglect over the four years to paediatricians in Leeds, an industrial city with a population of 750 000. In the latter half of 1988 additional numbers of paediatricians in the two major hospitals in the city became involved in seeing abused children and most of these children are included in the data.

Details of this larger group will be provided elsewhere in due course. Of the 130 physically and sexually abused children, there were 77 girls (mean age 5.7 years) and 53 boys (mean age 6.8 years). Sixty four (49%) of the children were aged less than 5 years (41 (31%) girls, 23 (18%) boys), 47 (36%) were 5-10 years (27 (21%) girls, 20 (15%) boys), 18 (14%) were 10-15 years (eight (6%) girls, 10 (8%) boys), and one girl was aged over 15 (fig 1).

Table 1 Numbers of physically and sexually abused children by year of diagnosis

Year	Non-accidental injury	Sexual abuse	Non-accidental injury and sexual abuse
1985	182	100	13
1986	207	237	35
1987	207	333	40
1988	173	279	42
Totals	769	949	130

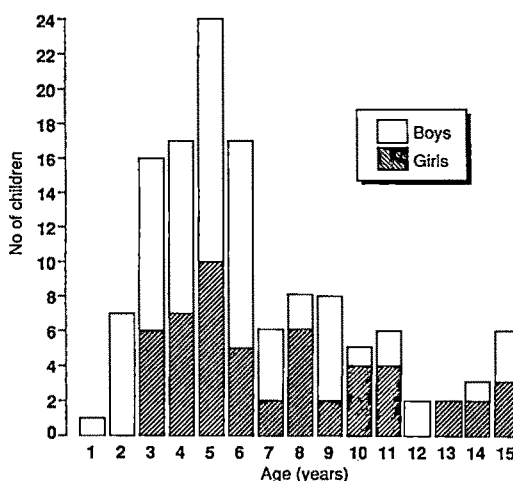


Figure 1 Physically and sexually abused children by age and gender at the times of diagnosis.

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The children presented differently and in three main ways. In 72 the child was referred because of physical injury, and evidence of sexual abuse was found from the history and examination. In 43 referral was prompted because of suspicion of sexual abuse, usually because of a disclosure or symptoms which might suggest sexual abuse (for example, recurrent vulval soreness, wetting, soiling, or inappropriate sexual behaviour). In these 43 children evidence of non-accidental injury was found when the child was fully examined. In a further 12 children physical and sexual abuse were diagnosed on separate occasions, which we were aware of at the time of seeing the child.

It was not part of this study to make detailed or exhaustive searches to see whether other incidents of physical or sexual abuse had been recorded elsewhere, possibly by other agencies. It is possible, therefore, that this figure underestimates the true frequency of non-concurrent physical and sexual abuse. In three children it was not possible to classify from the records what had been the mode of presentation.

Types of physical injury

Six children had fractures, including two with more than one fracture. These affected clavicle, skull, ribs, tibia, and femur. A total of 110 children had bruises: 70 had fewer than 10 bruises, 23 between 10 and 20, six between 20 and 30, and 11 over 30 in total number. Figure 2 shows the distribution of various sites in the children where bruises were found.

Bruising in sites commonly associated with non-accidental injury—notably the head, neck,

and face—was also found in these children but sites close to the genitalia included the thigh (n=71), paragenital (n=7), abdomen (n=19), and buttocks in 39 children. Bruising around the knees was noted in 33.

Bites were found in two children. Scratches, another common injury in these children, were noted in 38. Burns or scalds were present in 22. There were usually poorly or inadequately explained and of varying ages, including scars. Many were small and only detected after careful examination and questioning about suspicious lesions or scars. The sites were hand (n=7), thigh (n=4), genital/groin (n=4), leg (n=4), buttocks (n=2), arm (n=2), foot (n=2), and abdomen (n=1). It was not always possible to ascertain the cause of the burn, especially where it was old or healing. In these children cigarettes were involved.

Evidence of failure to thrive, as judged by weight below third percentile for age without the presence of organic disease, was found in nine children.

Evidence of sexual abuse

In 70 children there was a disclosure: partial in 29 and full in 41. We considered that a partial disclosure had been made when, as in the case of a 4 year old who had been hit across the face by his mother causing bruising, the child had been exhibiting sexually inappropriate behaviour in nursery, putting his penis between little girls' legs and kissing them in the vulval area. When asked the child said 'mummy does it'.

Historical evidence of oral sex was discovered in six children. Genital or anal physical signs seen in association with sexual abuse were present in 70 girls and 48 boys. In the girls, 59 had genital abnormality, 48 anal abnormality, and 37 both.

Abusers

In 1985 and 1986 detailed information was available on abusers from the investigation of police officers and social workers. Convictions were obtained in relation to 25% of children reported elsewhere.⁶ With the changing climate of opinion in the United Kingdom which took place in 1987/8, fewer convictions were obtained and the identity of the abuser was more effectively hidden. We therefore did not attempt to analyse figures over this period.

Data are presented, therefore, in relation to the 48 children in the two years 1985 and 1986. There were 53 abusers involved in the sexual abuse, and where the physical abuse was perpetrated by a separate individual, this has not been included. Thirty seven abusers were in the position of male parent figure, including natural father (n=21), cohabiting unrelated boyfriend (n=9), stepfather (n=6), and foster father (n=1). Mothers abused in five cases, sometimes with father and sometimes alone. Other abusers were: brother (n=3), family friend/neighbour (n=3), lodger (n=1), cousin (n=1), babysitter (n=1), and in two cases the identity was unknown.

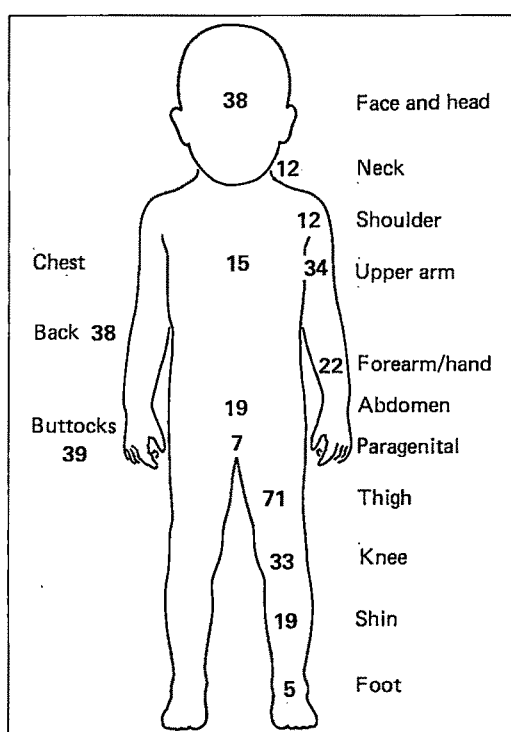


Figure 2 Distribution of bruises by site in 110 physically and sexually abused children. Figures refer to number of children.

Table 2 Fatal physical and sexual abuse

Case	Sex	Age (years)	Details
A	F	13.8	Abused by stepfather, including aggressive sadistic abuse. Anal and vaginal abuse. Death from strangulation. Mother also murdered and stepfather committed suicide.
B	F	1.2	Allegedly drowned in bath incident. Dry hair, circumoral petechiae. Failed to thrive with entry of stepfather into family. Old unrepresented fractured femur, grip mark bruises to knee. Grossly dilated anus. Previous suspicious burn in sibling. Siblings disclosed oral/anal abuse by stepfather.
C	M	3.9	Multiple bruises to face, head, neck, back, retinal haemorrhages and subarachnoid haemorrhage after violent shaking. His anus showed dilatation and tears which were later confirmed at postmortem examination. Cohabiting boyfriend was the abuser.
D	F	0.4	Multiple bruises including pinch marks over chest. Torn frenulum, retinal haemorrhages. Fractures skull and ribs. Labial fusion, multiple superficial anal tears with gross anal dilatation. Handicapped sibling had gross anal signs that resolved. Father admitted to physical but not sexual abuse.

Deaths

Four children died as the result of abuse. They ranged in age from 5 months to 13 years.

In the oldest child, the likelihood that she was being sexually abused had been recognised before her death and attempts had been made to separate her from her stepfather. Unknown to the professional agencies involved, she returned to the family home where she was again sexually assaulted and both she and her mother murdered by the stepfather, who then committed suicide.

Table 2 demonstrates further details of these cases.

Patterns of injury seen in physical and sexual abuse

CASE HISTORIES

Case 1

A 9 year old boy was referred by social services because of bruising to his face. He was short (height and weight 3rd centile). There were 30-40 bruises over face including eye, chin, jaw, fingertip bruising to top of right shoulder, a chain mark on wrist, and bruises to upper arms and back, chest, and thigh. His anus showed gross dilatation, loss of folds, and smooth thickened skin. After several months in a child protective environment he disclosed buggery by mother's cohabiting boyfriend, later retracting this and naming a neighbour.

Case 2

A boy of 2.5 years had suffered a previous incident of non-accidental injury and was being closely supervised by social service workers. He was brought to hospital with extensive subgaleal haemorrhage and numerous bruises over his face and trunk including fingertip pattern over

the lower back. In addition a recent burn on his scrotum was noted and 'kissing' burns on the medial side of either buttock close to his anus, which showed recent abrasions, a recent fissure, dilatation, and discharge secondary to proctitis. There were other burns on the posterior and lateral aspects of his thighs, ankles, foot, and neck, as well as petechial bruising to the dorsum of his penis.

Case 3

A 6 year old girl was referred to her family doctor by her grandmother, who had care at weekends, when she noted bruising to the child's face. There was bruising to her ear and cheek consistent with a hand slap. The child said 'mummy hit me because daddy came into my bedroom again'. She disclosed to the doctor that he had laid on top of her and touched her on her 'tuppence' (vulva) and rubbed 'it' (penis) on her. Hymenal tears were present.

Case 4

A 4 year old presented with a large bruise over the symphysis pubis. The history was of an unwitnessed kick in a playground, but previous physical abuse to a brother and the father's (who was in his 30s) suspected cohabitation with a 13 year old girl who had adopted the mother role in the family caused concern.

Two years later the child was raped. A previously dilated hymenal orifice and posterior vaginal wall tear which required sutures were found. There was bruising to symphysis pubis, outer thigh (pinch configuration), grip marks around knee, and a large bruise to inner upper thigh. The 13 year old girl's 18 year old brother admitted to the rape.

Case 5

A 6 year old boy had been persistently behaving in sexually inappropriate ways toward a female home care worker and was referred to a child psychiatrist. During play sessions he started to disclose that his mother, who was the sole parent, had been inserting her fingers into his bottom and hurting him. On examination he had a lax, reddened anus with congested veins and a deep circular and cratered burn on the back of one of his fingers which he said 'mummy did with a cigarette'.

Case 6

A 4.5 year old girl was brought to the accident and emergency department with facial bruising around the eyes, cheek, ear, and jawline after an alleged fall downstairs. The history was accepted and she was allowed home. The next day she returned with severe perineal bleeding from a tear, which extended from posterior vaginal wall across perineum to anterior anal wall. Bruising to her neck, anterior chest, inside upper arm as well as a laceration of her upper lip and fresh fingernail scratches to both lower thighs were additionally noted. The labia majora were bruised and swollen and there was

an anterior perianal haematoma. Her 3 year old sister showed signs of chronic anal abuse and both children had developmental language problems and gross behaviour disturbance. Although the identity of the abuser(s) was never definitely ascertained, both children later made disclosures within a child protective environment out of the family's care.

Discussion

Previous studies have mentioned the association of violent non-genital or anal injury in sexually abused children.³⁻⁴ Our data are consistent with one in six physically abused children also having been sexually abused and one in seven sexually abused children having been physically abused. Physical abuse as a presentation of sexual abuse occurred in one in 10 of our sexually abused children described elsewhere.⁵

Interestingly, the proportion of physically abused children who were also sexually abused appears to have risen from 7.1% in 1985 to 24.2% in 1988, suggesting that a more accurate figure might be greater than one in six as our ability to recognise sexual abuse increases.

In many cases the pattern of physical abuse is indistinguishable from the classical cases described in the literature over many years. In others, the presence of burns, grasp or pinch marks, or scratches around the lower body, genitalia, anus, thighs, knees, or buttocks would make one think of the possibility of a sexual motivation behind the assault.

Although we have not undertaken comparable analyses of injury location, Buchanan found in 251 abused children that the total number of injuries in particular sites were: forehead (n=37), around eyes (n=49), cheeks (n=114), mouth (n=10), lower jaw (n=18), ears (n=49), mastoid (n=11), arms (n=119), hands (n=7), legs (n=82), feet (n=4), chest (n=23), abdomen (n=16), back (n=60), and buttocks (n=52).⁶ His analysis included both sexually and non-sexually battered children. In his data a larger number of children have injury to the head and neck and in ours the legs and abdomen are more commonly involved.

Sexual abuse is defined as the involvement of dependent, developmentally immature children and adolescents in sexual activities they do not fully comprehend and are unable to give informed consent to and that violate the social taboos of family roles.⁷

While sexual abuse can undoubtedly occur within the context of a loving and caring relationship, it is the lack of meaningful consent that is central to the exploitation and abuse. Children are unable to consent to activities that they are unable to understand and for which they are developmentally unprepared. Children do not seek out or request or initiate sexual activity, although they may become involved in it as a means of fulfilling their needs for physical affection and contact.

It is the adult who exploits these needs and the child's weaker position for their own sexual gratification. In a sense all sexual abuse is violent because of the differential in size and power between the adult and the child. A young child

who experiences a man weighing 70 kg lying on top of her also experiences violence, although there may be no physical injury.

In most cases the adult is able to secure the child's 'cooperation' through threats, games, bribery, or trickery. In other cases, however, actual physical force is used to hold the child, force their legs open, or to stop them screaming. The abuser may also wish to keep the child quiet by threats backed up with physical violence or may punish the child's attempts to disclose. The resistive behaviours that some children develop—for example, soiling and wetting, running away, fire setting, and also the sexually inappropriate behaviour—may be discouraged by punishment or threat.

For some abusers the association of sexual arousal with aggression coupled with the need to maintain the level of arousal through escalating violence, leads to serious injury or to the child's death. Hallmarks of this pattern of abuser are the presence of sadistic premeditated injuries such as burns or scalds, which should provide warnings of serious risk if the child is not immediately protected by physical separation from the abuser.

While public attention has been directed through the media to violent and fatal sexual assault by strangers who abduct the child, it should come as no surprise that similar assaults can also occur in the home by caregivers. We have been told of cases in which the association of sexual abuse and child death within the home has occurred (A Bentovim, personal communication).

The findings in this study indicate that professionals involved in assessing physically abused children must always be aware of the possibility of sexual abuse. While this may be obvious when the injury is in the perineal or genital area, and there are guidelines for assessing which of these injuries may have arisen non-accidentally and which accidentally,⁸ when injuries occur elsewhere the association may not be considered. It is important, therefore, that in all cases of suspected physical abuse the physician should undertake a detailed genital and anal inspection and spend time (or arrange for others to do so) exploring with the child the possibility of sexual abuse. It is also important to examine for both physical and sexual abuse,⁹ including a full paediatric history and inquiry for symptoms that could be of relevance.

While it is not within the remit of this paper to discuss details of the management of physically and sexually abused children, it is obviously of crucial importance to recognise when there is a sexual element in the abuse as management may be considerably affected. Plans for future treatment and rehabilitation will be influenced by the nature of the abuse the child has suffered. It is likely that the legal consequences will also differ significantly and in this we agree with other authors.³

More work is needed by pathologists on the postmortem findings of sexually abused children. Many of the findings that have been described elsewhere are dynamic, functional, and as such not available to the pathologist. We note the caution that must be taken in interpret-

ing postmortem anal dilatation,^{10 11} but further studies are urgently needed. In our cases other findings led us to a diagnosis of sexual abuse in these children.

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Surveillance for anaemia: risk factors in patterns of milk intake

A F Mills

Abstract

The association between patterns of milk intake and anaemia was studied during a surveillance programme for iron deficiency anaemia. Children aged 8-24 months were examined when they attended a routine immunisation clinic. Haemoglobin was measured on finger prick blood samples using a portable haemoglobinometer, and a dietary questionnaire was completed, with special emphasis on the type and volume of milk intake and the age at which whole cows' milk was introduced.

Anaemia (defined as a haemoglobin concentration of <110 g/l) was diagnosed in 33 children (22%) and was more common among children who were not white. Continued feeding with breast milk and the early introduction of whole cows' milk were associated with a significantly higher prevalence of anaemia. No child taking formula milk was anaemic. Asian children drank significantly more milk a day than other groups, but there was no correlation between daily milk intake and haemoglobin concentration.

Iron deficiency anaemia is one of the most common deficiency diseases in children in developed countries. It affects particularly those living in poor socioeconomic circumstances, and children of immigrant communities—for example, those from Asian communities are commonly affected.^{1 2} The deficiency is in most cases of dietary origin, and probably results from inadequate weaning. Many affected toddlers take diets consisting of starchy solids and large amounts of whole cows' milk,³ which reduces their intake of iron containing foods. A further factor may be that gastrointestinal bleeding may be caused by whole cows' milk when introduced to children under the age of 6 months.⁴ Iron for-

tified formula milk is likely to protect against iron deficiency anaemia.⁵ Breast milk contains iron in a highly bioavailable form, and provides the infant's iron requirements for the first six months.⁶ If factors such as the type and volume of milk intake can be correlated with the incidence of anaemia, such measurements may be useful in detecting those at particular risk of iron deficiency anaemia.

The aim of this study was to survey the type and volume of milk intake, and the age at which whole cows' milk was introduced into the diets of children aged 8-24 months, and to examine the association between these factors and the prevalence of anaemia.

Patients and methods

A programme to screen toddlers for anaemia was set up in Waltham Forest Health Authority in east London, with the aim of screening all children aged 8-24 months attending one of five routine immunisation clinics for their third diphtheria, pertussis, and tetanus, or measles, immunisation between December 1987 and March 1988. All the clinics were grouped in a small area in the south of Waltham Forest in which a large proportion of the families are first or second generation immigrants. The parents were approached when they attended the immunisation clinic and were given a written and verbal description of the programme. The written description was available in English, Urdu, Bengali, Gujarati, and Punjabi. An interpreter was always available. If parents agreed, they gave written consent and their child was seen immediately after the immunisation. Siblings of the children were also seen if the parents wished, but were not included in this study. The programme was in two parts.

Firstly, a questionnaire was completed by the doctor, and details of parents' racial group,

Table 1 Details of 148 children studied

Ethnic group	Total No of children	Mean (SD) haemoglobin concentration (g/l)	No (%) of children anaemic	Mean (SD) milk intake (ml/24 hours)
White	52	119.9 (9.3)	9 (17)	496 (248)
Asian:	62	116.2 (10.9)	16 (26)	740 (307)
Pakistani	48			
Bangladeshi	2			
Indian	12			
Other:	34	115.1 (9.3)	6 (18)	548 (289)
Caribbean	18			
West African	5			
Southeast Asian and Chinese	5			
Mixed race	6			

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Table 2 Number taking each milk type related to age in each racial group

	White: age range (months)				Asian: age range (months)				Other: age range (months)			
	8-11	12-14	15-17	18-24	8-11	12-14	15-17	18-24	8-11	12-14	15-17	18-24
Breast milk	1	1	1	0	1	2	1	0	3	0	0	0
Formula milk	2	2	1	0	3	0	0	0	1	1	5	0
Whole cows' milk	9	9	21	5	14	14	16	10	2	6	10	6

One Asian child (previously having had whole cows' milk) was taking no milk at time of study.

Table 3 Age (months) when whole cows' milk was introduced

Age (months)	No (%) taking whole cows' milk		
	White (n=39)	Asian (n=50)	Other (n=22)
4	1 (3)	2 (4)	1 (5)
6	8 (21)	16 (32)	6 (27)
8	21 (54)	30 (60)	11 (50)
10	27 (69)	39 (78)	13 (59)
12	30 (77)	42 (84)	16 (73)

Eleven mothers could not remember when whole cows' milk was introduced. Twenty five were on other milks, and one child was taking no milk.

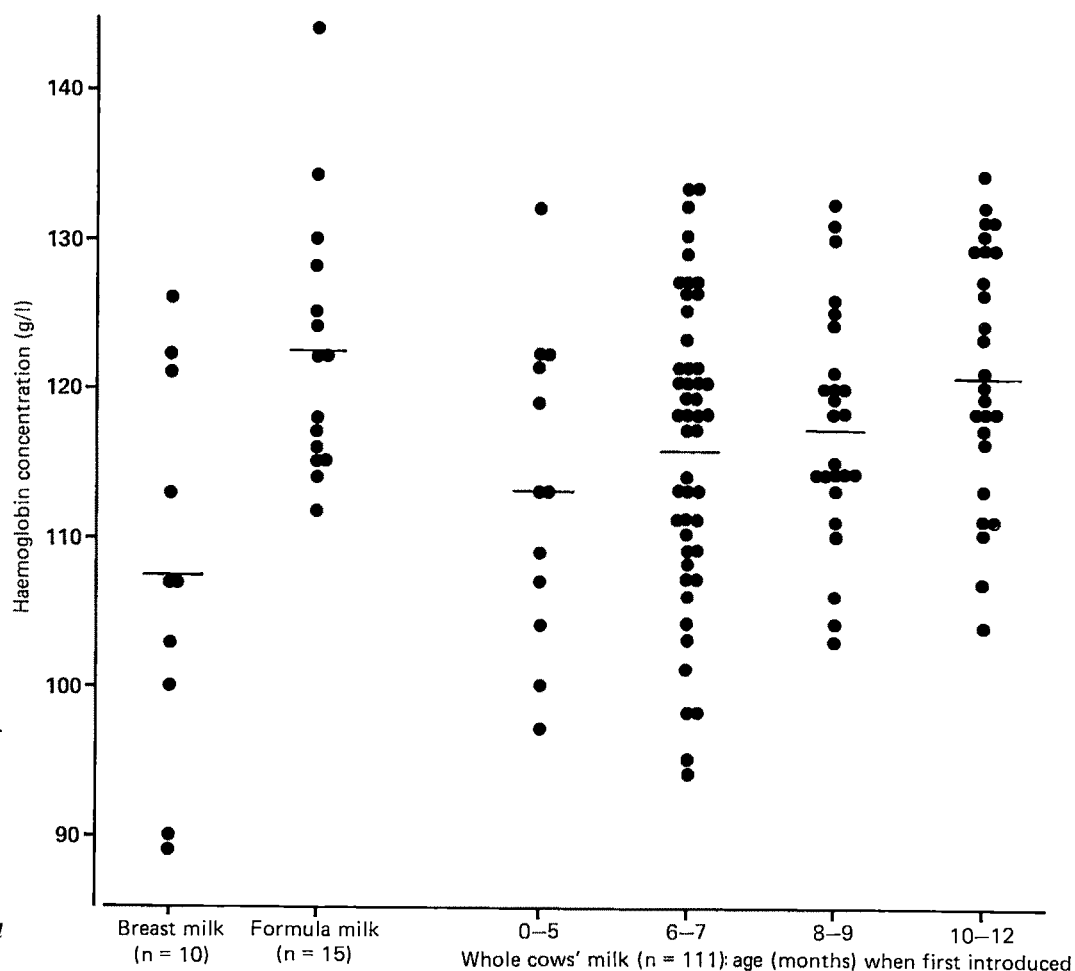
child's age, type and daily average volume of milk intake, and age at which whole cows' milk was introduced were recorded. If more than one type of milk was being taken, the milk that predominated was noted. Any personal or family history of anaemia was recorded and any courses of oral iron were recorded. An informal assessment of diet was also undertaken. Parents were questioned about the amount of meat, vegetables, sources of vitamin C, starchy foods, sweets, and crisps their child ate during an average day.

All children were classified into one of three racial groups: white (European), Asian (from the Indian subcontinent), and others (Afro-Caribbean, south east Asia and Chinese, and mixed race). Most of the Asian children came from Moslem families originating from Pakistan.

Secondly, a finger prick blood sample was taken, and the haemoglobin concentration was measured using a 'HemoCue' haemoglobinometer (Clandon Scientific).⁷ Further capillary blood was collected into a bottle containing EDTA for subsequent analysis if indicated.

Those found to be anaemic (defined as a haemoglobin concentration of <110 g/l)⁸ were referred to a paediatric clinic for further investigation and treatment. Those who were considered to be having an inadequate diet, despite the haemoglobin concentration being >110 g/l, were given nutritional counselling and followed up in the community clinic.

We tried to screen all eligible children. Of those offered the test, 65% agreed immediately. Some returned on a subsequent day. Common reasons for refusal were that parents felt that a



further painful procedure after immunisation was unfair and others felt that their children were unlikely to be anaemic.

Statistical evaluation was by unpaired Student's *t* test and χ^2 with Yates's correction. Ethics committee approval was obtained.

Results

A total of 150 parents gave consent for their children to take part in the scheme. Two children were subsequently found to have β thalassaemia trait and were excluded from the study. There were 73 boys and 75 girls. Table 1 shows the mean haemoglobin concentrations and mean daily volumes of fresh or formula milk in each racial group. Asian children drank significantly more milk than both white children ($p < 0.001$) and those from other groups ($p < 0.01$). The white children had a slightly higher mean haemoglobin concentration and a lower prevalence of anaemia than the other two groups, but these are not statistically significant.

Table 2 shows the age distribution and main type of milk being taken at the time of screening according to age in each group. All children over 18 months mostly drank cows' milk. Table 3 shows the age at which children had first been

given fresh cows' milk; 11 mothers could not remember this age. The mean (SD) haemoglobin from these 11 children was 115.5 g/l (10.3).

Figure 1 shows the association between the type of milk taken and haemoglobin concentration. The children taking formula milk had a significantly higher mean haemoglobin concentration than those taking whole cows' milk ($p < 0.05$), or breast milk ($p < 0.01$). No child taking formula milk was anaemic. The association between the age at which fresh cows' milk was started and haemoglobin concentration is shown. Mean haemoglobin concentration rose with increasing age of introduction of whole cows' milk. Anaemia was significantly more common among those starting whole cows' milk before the age of 8 months compared with those starting after this age. ($\chi^2 = 5.67$ $p < 0.05$).

Figure 2 shows the association between the volume of milk taken during each 24 hours and haemoglobin concentration. The greater volume of milk taken by Asian children is shown. There was no correlation between the daily milk intake and haemoglobin concentration, although anaemia was more common in Asians who drank more than a litre a day compared with those who drank less; this was, however, not statistically significant.

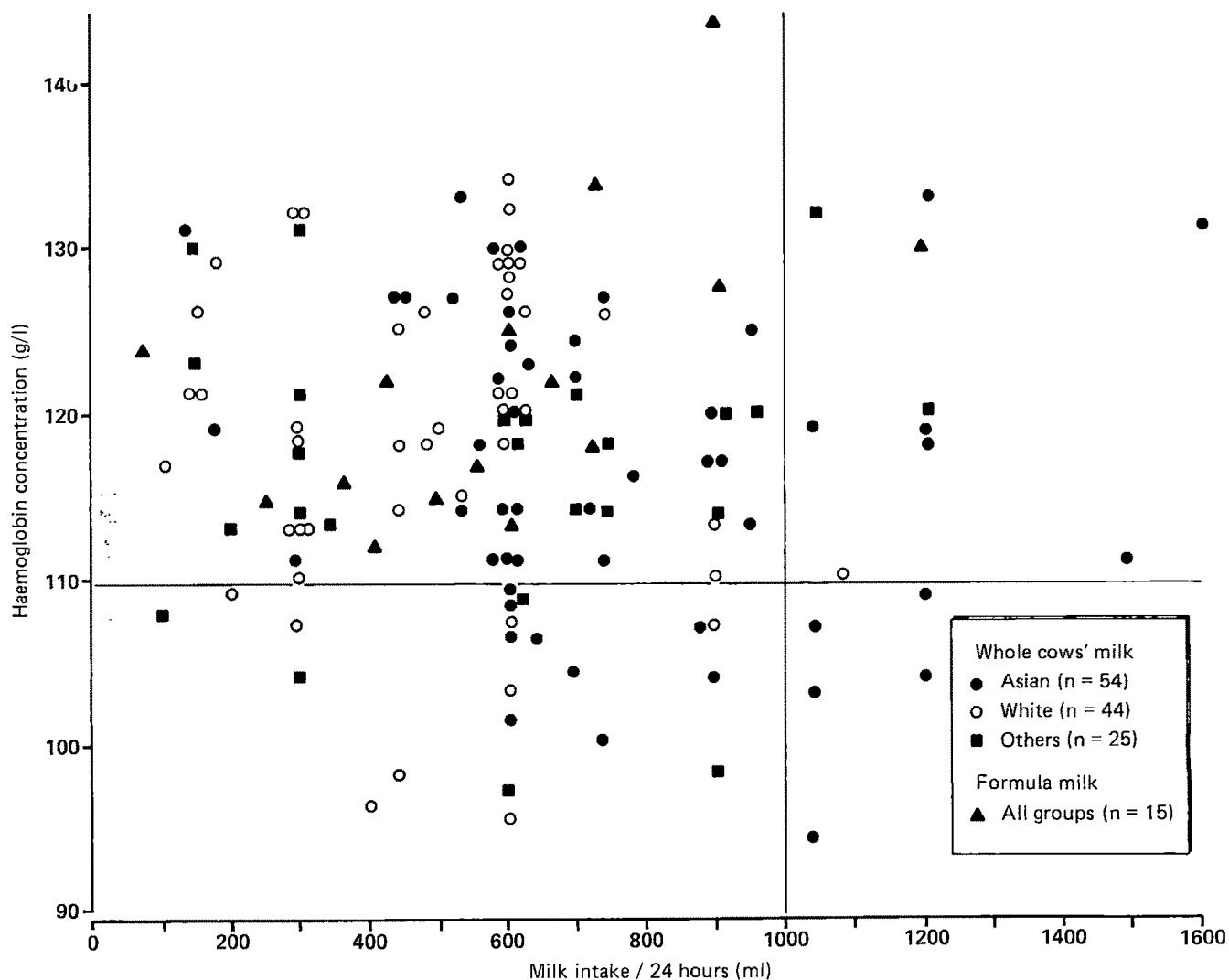


Figure 2 Association between volume of milk taken/24 hours and haemoglobin concentration by racial group. Ten children were receiving breast milk at the time of the study and are not included.

Discussion

Whether there is a need for a comprehensive screening campaign for iron deficiency anaemia is controversial.⁹ The finding that cognitive development of affected toddlers may be slowed has led some to advocate for a programme in groups that are at risk.¹⁰

The results of this study show that surveillance for iron deficiency anaemia using a routine finger prick sample is possible in a community paediatric clinic. Anaemia was found in 22% of our patients, and there was a higher prevalence among the non-white population. This is similar to results from Bradford and Birmingham.^{1,10} The use of haemoglobin concentration to select those likely to be iron deficient means that a number of false negatives will occur. The surveillance programme did, however, include informal dietary assessment with counselling, and follow up for those taking a poor diet. This aspect of the programme helped to ensure that children with false negative results on blood testing at least had careful attention paid to their diets.

The age of the group studied was well above the age when weaning and the introduction of solids containing iron usually takes place. To detect those at risk of iron deficiency it is more logical to undertake a formal dietary assessment and analysis. This is, however, a skilled and time consuming process and is not suitable as a screening procedure. This study aimed to look at simple and easily assessed dietary measurements.

The higher mean concentration of haemoglobin in formula fed infants is presumably because of the iron fortification in these milks. This observation has been made previously, but is important.¹¹ Prolonging formula feeding may be good advice to those parents who have difficulty in establishing their infants on mixed feeding.

The significantly lower haemoglobin concentration among those who were breast fed is interesting. The amount of iron in breast milk, although low, is extremely well absorbed and breast feeding is said to protect against iron deficiency anaemia in the first 6 months.¹² Over this age, however, some form of additional iron intake is required in order to replace depleted iron stores. More information is needed about the success of weaning these infants, as this may remain a problem associated with prolonged breast feeding.

Early introduction of cows' milk predisposes to iron deficiency.⁴ Cows' milk is a poor source of iron and it may cause gastrointestinal bleeding, particularly in the immature gut. This may explain the rise in mean haemoglobin concentration with increasing age when whole cows' milk was first introduced. Other factors may

include the length of time for which formula milk was given before changing to cows' milk, and the quality of weaning solids given to those who started cows' milk at an early age.

Clinical experience indicates that those with iron deficiency anaemia often drink large volumes of milk. There was no clear correlation between the quantity of milk and the haemoglobin concentration, although anaemia is more common among those drinking over a litre of milk a day. Presumably a large milk intake does not necessarily result in an iron deficient diet.

The results of this study show that routine finger prick samples are practicable for use in a community clinic. Anaemia is common, and is usually caused by iron deficiency. Prolonged breast feeding and early introduction of cows' milk are associated with anaemia, and the continued use of formula milk protects against anaemia.

No account was taken in this study of the role of birth weight, or the age and quality of weaning. More detailed information is required from a prospective study. In the meantime early introduction of whole cows' milk should be discouraged, and good weaning practices (including introducing mixed solids and vitamin C) should be promoted. Formula milk should be continued up to the age of 1 year—and possibly beyond—for those children that are not well established on a good mixed diet. Those that continue to breast feed after 6 months should have particular attention paid to weaning. Screening for iron deficiency should be considered in those areas with large immigrant populations.

I thank Dr P Thompson, Dr N Meadows, Mrs M Slevin and the clinic administrators, and Dr C D'Silva and the staff of the haematology department, Whipps Cross Hospital.

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Oculokinetic perimetry for the assessment of visual fields

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Abstract

The visual fields of 13 children aged 7 to 16 (mean 10.7 years) were assessed by oculokinetic perimetry (OKP), a technique where the field of vision is tested at reading distance using a simple chart, and the results compared with conventional Goldmann perimetry. Cooperation with testing was greater for OKP than Goldmann perimetry and in some cases OKP was better correlated with clinical findings. The advantages of visual field assessment by OKP for children are the close proximity of observer and child, the absence of the requirement for prolonged fixation, and the inexpensiveness and portability of the testing equipment. The disadvantages are movements of the head, with variability in the distance from the target, and the limitation to the central 25 degrees of the visual field.

Assessment of visual fields in children is fraught with problems. Frequently, conventional methods of perimetry seem daunting to a child. If there are difficulties with cooperation unreliable assessments result and even experienced perimetrists may have difficulty in making meaningful assessments. Many tests can only be carried out in suitably equipped departments.

Recently Damato has devised a novel method of assessment of the central 25 degrees of the visual fields that is not reliant on expertise or expensive equipment.¹ The eye moves around a stationary central target, and this method is referred to as oculokinetic perimetry (OKP). The test chart consists of a white tangent chart with a series of light blue fixation targets numbered from 1 to 100 distributed within 25 degrees around a central black test stimulus. These numbers are placed in 16 meridians at 2.5 to 5.0 degree intervals. The patient fixes on each number in turn and determines whether the central target is also visible. In this way, a map of the central visual field can be recorded by noting those points where the central stimulus is not visible. When the test is completed the record sheet is inverted to render the results comparable with those obtained by conventional perimetry. This method had been found to be reliable both in adult patients with glaucomatous field loss and in patients with a range of neurological diseases.¹⁻³

This study has attempted to assess the suitability of this simple method for the examination of the visual fields in school age children with a range of ophthalmic and neurological disorders.

Patients and methods

Thirteen consecutive children aged 7 to 16 years (mean 10.7 years) who were referred for visual field testing were assessed by Goldmann perimetry by an experienced perimetrist and then by OKP by a previously inexperienced observer who was unaware both of the results of Goldmann perimetry and of any field deficit expected on clinical grounds.

OKP was carried out in a busy clinic setting with no special lighting or equipment. The child was seated 33 cm from the disposable paper test chart which was pinned to a board at eye level. The test was presented as a game where the child was required to tell the observer of those points where it was possible to see both the number on the chart and the central stationary target dot simultaneously. The child was told that some spots were not meant to be seen and the game was to find which ones. The reliability of answers was checked by covering the central dot with a white card and slowly uncovering it. During this the child was asked to respond the instant the dot became visible. Any position on the chart suspected of giving unreliable results was repeated and checked in this way.

Children wore spectacles for both tests when a refractive error was present.

Each child was examined by an ophthalmologist who had access to the child's ophthalmic and medical history and who graded the correlation between Goldmann fields, OKP, and clinical findings as good, moderate, or poor.

Results

The clinical details of the subjects and the results of this study are outlined in the table.

Three children had normal Goldmann fields (cases 5, 10, and 11). These were judged to correlate well with both the OKP fields and the clinical findings. The blind spots were successfully determined for all three children (fig 1). In four children (cases 2, 3, 4, and 13) abnormal Goldmann fields were demonstrated, with a good correlation with the OKP fields and with the expected field defect. In hemianopic defects macular sparing was much better demonstrated by OKP (fig 2).

Two children showed constricted visual fields by Goldmann perimetry (cases 1 and 6), this was consistent with the clinical diagnosis, which was not well demonstrated by OKP. Case 1 showed enlarged blind spots by Goldmann perimetry that were not consistent with clinical findings; OKP showed normal sized blind spots.

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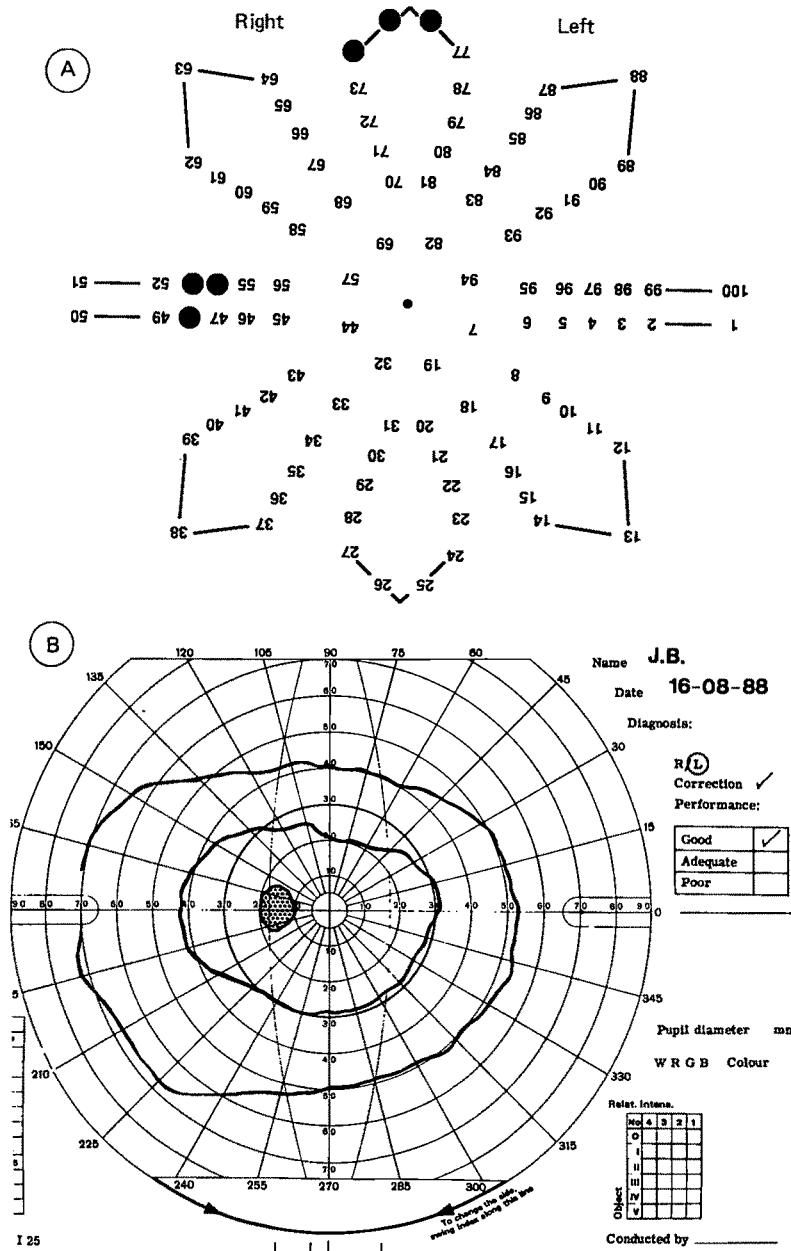
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Clinical diagnoses and correlation with visual field assessment

Case No	Age (years)	Sex	Disorder	Acuity	Goldmann fields	Goldmann/clinical correlation	OKP/clinical correlation
1	9	F	Postencephalitis	Right 6/6 Left 6/6	Peripheral constriction, enlarged blind spots	Good	Moderate
2	11	F	Right temporal lobe mass (after meningitis)	Right 6/18 Left 6/18	Gross constriction	Moderate	Moderate
3	8	F	Left lateral ventricle choroid papilloma (after surgery)	Right 6/6 Left 6/6	Right homonymous hemianopia	Good	Good
4	14	F	Chiasmal glioma (after radiotherapy)	Right 6/5 Left 6/60	Bitemporal hemianopia	Good	Good
5	14	M	Neurofibromatosis, optic nerve glioma	Right 6/6 Left 6/6	Normal	Good	Good
6	8	M	Dominant optic atrophy	Right 6/18 Left 6/60	Peripheral constriction	Good	Poor
7	14	F	Apert's syndrome	Right 6/6 Left 6/12	Tunnel fields	Poor	Good
8	8	M	Functional monocular diplopia	Right 6/9 Left 6/6	Irregular constriction	Poor	Poor
9	11	F	Facial haemangioma with left hemisphere infarct	Right 6/36 Left NPL	Spiralling constriction	Poor	Moderate
10	16	F	Neurofibromatosis, optic nerve glioma	Right 6/5 Left 6/5	Normal	Good	Good
11	9	F	Neurofibromatosis, chiasmal glioma	Right 6/5 Left 6/5	Normal	Good	Good
12	7	M	Neurofibromatosis	Right 6/6 Left 6/6	Failed to complete either test		
13	11	M	Craniopharyngioma (after surgery)	Right 6/9 Left NPL	Hemianopia	Good	Good

NPL, no perception of light.



One child (case 7) showed constricted fields of less than 5 degrees by large and small targets by Goldmann assessment but OKP was normal; this correlated well with the clinical findings.

Two children (cases 8 and 9) had functional visual complaints diagnosed. Case 8 complained of double vision in one eye for which there was no apparent cause. Goldmann and OKP fields were abnormal and correlated poorly with each other. Case 9 suffered a left hemisphere infarct after embolisation of a facial haemangioma three years previously and presented with a sudden diminution of vision in her remaining seeing eye. There was no apparent cause for the recent deterioration in vision; confrontation fields at 1 metre and 6 metres showed tunnel vision and Goldmann fields showed spiralling. OKP, however, demonstrated a right hemianopic defect with peripheral constriction in this eye that was consistent with the clinical findings of mild optic atrophy and the appearance on computed tomography of a left hemisphere infarct.

Case 12 failed to complete either Goldmann or OKP field assessments because of emotional lability.

In summary, Goldmann and OKP field assessments were judged to correlate well in seven cases. In two cases OKP failed to demonstrate moderate peripheral constriction of fields. OKP was assessed as giving a more reliable assessment of field than Goldmann perimetry in two cases, one in a child with a normal field of vision and one in a child with hemianopia. One child with functional visual complaints had unreliable assessments by both techniques and one child failed to complete either test.

Figure 1 Normal central visual field and blind spot of the left eye of case 11 as determined by (A) OKP and (B) Goldmann perimetry. The OKP field is inverted to ease comparison.

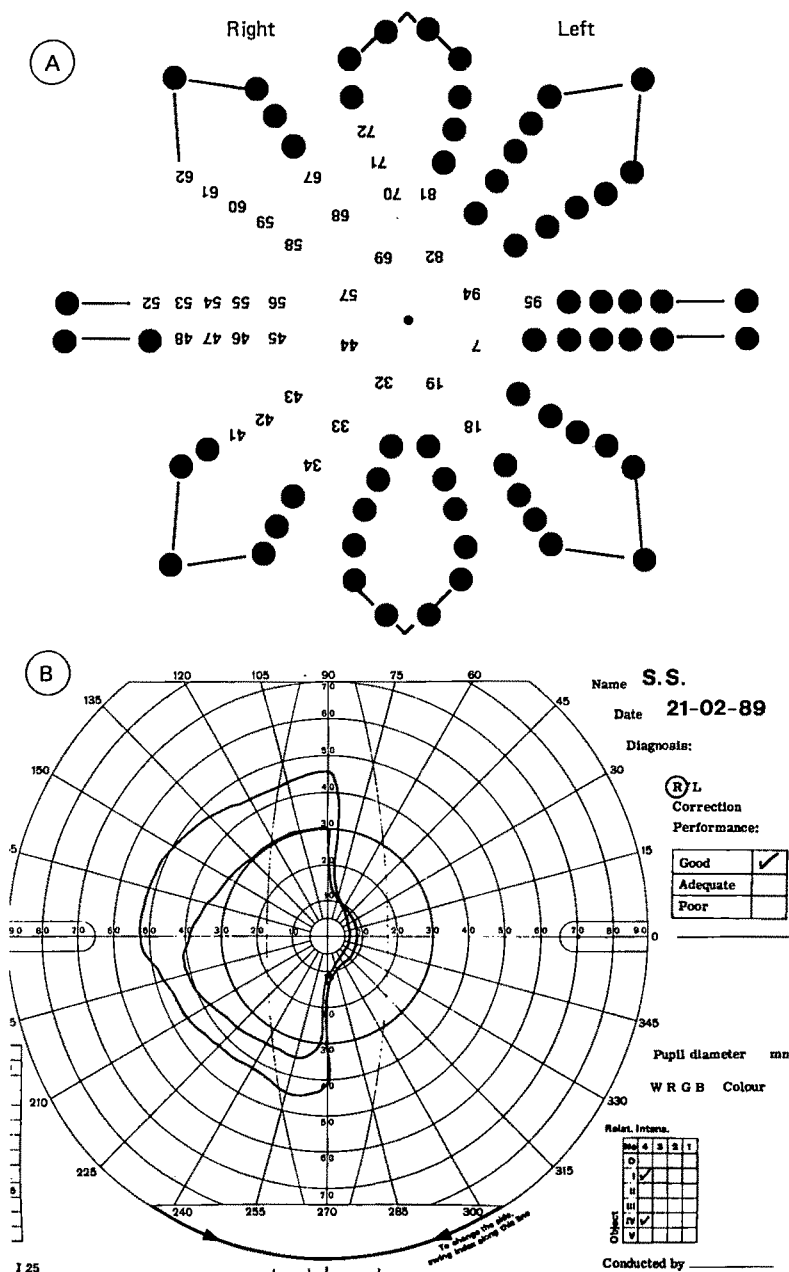


Figure 2 Case 13: hemianopia in the only seeing eye showing peripheral constriction; (A) OKP demonstrates macular sparing and (B) Goldmann perimetry. The OKP field is inverted to ease comparison.

Discussion

The Goldmann perimeter is a well accepted method of testing the visual fields in adults. It has the advantages of providing good head fixation, variable target sizes and intensities, and of assessing the peripheral visual field. The use of this machine is far from ideal when testing children, however, as it can easily frighten and alienate a child with subsequent breakdown of cooperation so necessary for a useful assessment of visual field. Inattentiveness to the fixation target is a major drawback when applying this test to children.

OKP has the advantages of simplicity, inexpensiveness, and portability. There is no requirement for a skilled perimetrist and it can

be carried out in the normal clinical setting as the variation in ambient illumination does not affect the result.³ There is a reduction in the sources of fear and anxiety as the child and the observer are not remote. This proximity of the tester allows better assessment of the psychological response to the test and may give a better indication of the child's cooperation and the reliability of the test. Perhaps the greatest advantage of this method is that the child does not have to fixate one spot for any length of time.

Head movement and fidgeting are a difficulty with variability of distance from the chart so that a less accurate assessment of visual fields by OKP is likely when applied to children rather than adults. This can be seen in hemianopia where rotation of the child's head results in a field which transgresses the vertical meridians. Furthermore, there is a tendency for some children to strive for a perfect record in the test. This can be overcome by explanation that there may be some areas on the chart where it will not be possible to see both the number and the central dot together and that it is important for the child to find where these areas lie. A further drawback with this method is that it only examines the central 25 degrees of field.

In two cases in this study OKP was considered to give results which correlated better with the clinical findings than Goldmann perimetry. This, of course, begs the question 'which is the gold standard?' This can be difficult to ascertain in paediatric practice and no method currently available can be regarded as ideal. It is for this reason that OKP and Goldmann perimetry were not directly compared in isolation—both were also compared with the clinical impression. However, a situation where a direct comparison between two methods of perimetry may be of value is in the detection of functional field loss.

The present format of OKP possibly does not fulfil its true potential for the examination of children. The use of 100 numbered points could be modified to use fewer points as some children at the end of the test found it slightly tedious. The substitution of symbols for the numbers may be one adaptation that could prove useful in maintaining a child's attention. With these modifications, OKP could be of use in screening of visual fields in children. Further studies are required to assess the reliability of the test in longitudinal studies of changes in field defects.

We are indebted to Mr D Taylor and Dr B Damato for their advice on conducting this study.

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Postmortem demonstration of intrapulmonary arteriovenous shunting

M J Wilkinson, D G Fagan

Abstract

The measurement of the pressure required to drive a 2% solution of gelatin across the pulmonary vascular bed of a group of 49 infants dying suddenly at less than 44 weeks' post-natal age, has shown the presence of low pressure arteriovenous shunting in 30 cases (61%). Injection of polymethylmethacrylate beads in three cases has demonstrated that the vessels that form the shunts are up to 60 μ m in diameter. The presence of vessels allowing shunting at pressures as low as 0.1 kPa (1 cm H₂O) could severely compromise the gas exchange function of the lung.

The syndrome of prolonged expirational apnoea is well recognised.¹ In this syndrome children may rapidly develop very profound arterial hypoxaemia after relatively short periods of apnoea.² It has been postulated that this hypoxaemia is due to the sudden development of intrapulmonary arteriovenous shunting.

It is a commonly held belief that there is no anatomical basis for the shunting, but it is observed at ages by which the foramen ovale and the ductus arteriosus have closed. In live children exhibiting shunting of this type echocardiography has been used to demonstrate the absence of intracardiac shunts and that the ductus arteriosus is closed.³ Subsequent necropsy confirmed the closure of the ductus but the shunting remained unexplained.

The belief that there is no anatomical basis for the shunting appears to be based on the work of Hislop and Reid who described the development and anatomy of the pulmonary vasculature in a group of children with ages ranging between 3 days and 11 years but found no evidence of shunts.⁴ Their method outlined the pulmonary vessels by injection of a concentrated solution of gelatin (25%) into the pulmonary artery of previously frozen lungs. The vessels were assessed on radiographs of the lung with limited histology. Vessels down to 15 μ m in diameter were filled with the mixture but no gelatin was seen in the pulmonary capillaries or in the pulmonary veins.

We used a similar technique to Hislop and Reid with a less concentrated solution and lower injection pressure in fresh lungs and found that in some cases the injection mixture flowed freely from the pulmonary vein. Histologically gelatin can be seen in the pulmonary veins, occasional capillaries, and airspaces.

Material and methods

Since 1985 we have been injecting the pulmon-

ary arteries with a solution of gelatin to study the development of the pulmonary vasculature. In some cases we noted that the gelatin flowed freely from the pulmonary vein, so we began to measure the pressure required. The fresh lungs of 49 infants up to 44 weeks' old, whose deaths had been referred to the coroner, were used in this study. All the infants had died to some degree unexpectedly both in hospital and at home. The Emery system of classifying infant death was used.⁵ In this class A are infants with a known fatal illness who are expected to die; class B are infants with a curable but potentially life threatening illness that may be treated, class C are infants with antemortem or postmortem evidence of minor illness who die unexpectedly, and class D are infants with little or no post-mortem evidence of disease to explain death. It must be emphasised that the classification is based on findings at necropsy and on examination of subsequent histology. Thus significant but unexpected findings are classified as for the disease, not the state of apparent wellbeing of the infant before death.

The thoracic contents were removed intact, the right lung isolated, and the right pulmonary artery cannulated. A 50 ml syringe was connected by a three way tap to the cannula, with the third arm connected to a water manometer. A mixture of barium sulphate and 2% gelatin was injected through the cannula into the artery. The pressure required to obtain a free flow of the mixture from the pulmonary vein was noted.

In three cases one lobe of the left lung was cannulated and a separate gelatin mixture containing polymethylmethacrylate beads with diameters up to 64 μ m in diameter injected. The mixture passing across the pulmonary vascular bed was collected from the left atrium thereby ensuring that the outflow sample was not contaminated by material from the inflow sample. The size of the beads was measured using a Kontron videoplan image analyser.

In two cases the right lung was injected immediately after the necropsy, the left was kept for either 24 or 36 hours at 4°C before

Results of pressure measurements in 49 cases studied (pressure in kPa)

Emery grade ⁵	Pressure/No of cases showing shunting			
	≤0.5	0.6-1.0	1.1-2.0	>2.0
A	3	0	2	1
B	4	3	1	2
C	10	6	6	5
D	0	4	2	0

Normal pulmonary diastolic pressure=7.5 mmHg (1 kPa or 10 cm H₂O).

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injection. No significant alteration in shunt pressure was observed.

In two cases with very low shunt pressures numerous serial sections were cut. No unequivocal abnormal shunt vessels were identified and it was hard to trace continuity between arteries and veins in vessels of the required size.

Results

In the six grade A cases the causes of death included: trauma, pneumonia, bronchopulmonary dysplasia, and congenital heart disease. In the 10 grade B cases they included: mening-

ococcal infection, tracheobronchitis, and viral and bacterial pneumonias. In the 27 grade C cases there were mostly early infective changes in the lung frequently with positive viral and bacterial cultures. In the six grade D cases only minimal findings were made at necropsy. These cases often had with positive viral and bacterial cultures with major organisms.

The perfusion pressure and some details of the patients studied are detailed in the table. Thirty of the cases showed perfusion at <1 kPa (<10 cm H₂O) with 19 at >1 kPa.

The presence of shunting vessels has been inferred in those cases where the perfusion pressure was <1 kPa (approximately equal to pulmonary diastolic pressure). In some of the cases there were only minimal findings at necropsy.

The group of cases in which shunting vessels were shown has a very similar distribution of Emery class to the group in which shunting vessels were not shown. The three cases in which beads were also injected are indicated with an asterisk. Measurement of the beads in the effluent is shown in fig 1. Large numbers of beads up to $40\text{ }\mu\text{m}$ in diameter pass through with occasional beads up to $55\text{ }\mu\text{m}$ in diameter. Histological assessment of the lungs showed the presence of gelatin mixture in small intra-acinar non-muscularised and muscularised vessels. Figure 2 shows beads up to $50\text{ }\mu\text{m}$ in diameter in venules and veins.

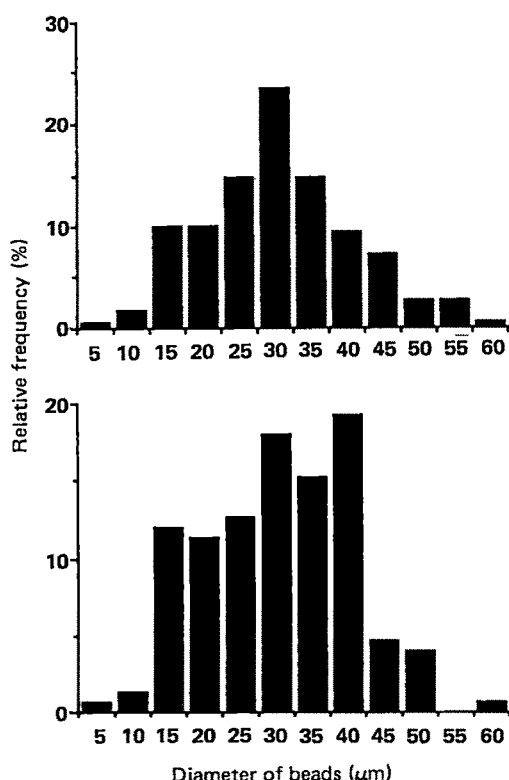


Figure 1 Graph showing the relative frequency diameter of beads in the injected material (upper graph) and in the material collected from the left atrium, (lower graph) in case 3.

Discussion

The initial impression of a group of cases in which venous return occurs at a low injection pressure is confirmed by the data in which the perfusion pressure was measured. The normal pulmonary diastolic blood pressure is around 7.5 mm Hg (1 kPa or 10 cm H₂O). In 30 of our 49 cases the flow occurred at a pressure less than this. In life this would allow the flow of blood across the lung at a very rapid rate even during diastole. These findings clearly demonstrate the presence of intrapulmonary arteriovenous shunting.

The injection of beads and measurement of the diameter of those beads able to pass through the vascular bed confirms that shunting vessels are present. The maximum diameter of the beads in the effluent from case 3 is about $55\text{ }\mu\text{m}$ but the size that significant numbers pass through is about $40\text{ }\mu\text{m}$. The diameter of the normal pulmonary capillary is less than that of a red cell ($7\text{ }\mu\text{m}$).⁶ It is inconceivable that a pulmonary capillary will stretch to increase its diameter by 2000%. Thus shunting vessels must be present in the lungs of these children.

Histological assessment of the lungs showed that although gelatin is present in the pulmonary veins, most of the capillaries are ruptured and the gelatin has passed into the airspaces. Beads are seen in the pulmonary veins, but not

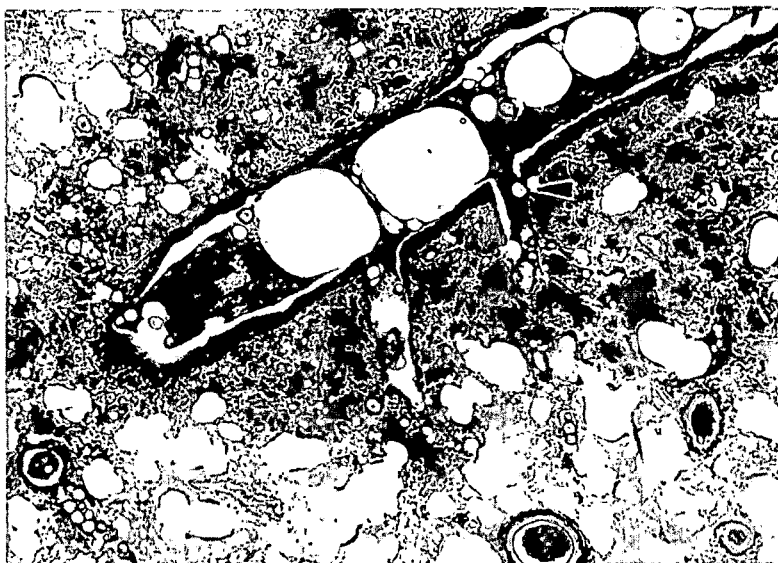


Figure 2 Section of lung showing beads up to $50\text{ }\mu\text{m}$ in diameter in veins and venules (arrowed). The section is $10\text{ }\mu\text{m}$ thick, illumination has been adjusted to give interference that highlights beads. (Elastin picro-sirius red $\times 62$.)

in the capillaries and only rarely in the air-spaces. Thus the histological findings support the observation that there are arteriovenous shunting vessels in the lung.

The demonstration of these arteriovenous shunts appears to be in conflict with the finding of Hislop and Reid.⁴ However, there are significant differences between our methods and theirs. Hislop and Reid studied lungs from 18 cases collected over a five year period; all the children were defined as normal with death due to accident. The ages ranged from 3 days to 11 years; although the ages of the cases is not stated, it is unlikely that there was a large number of infants under the age of 8 months. In their study, after removal from the body, the lungs were kept at a temperature of -2°C for an undefined period, and then thawed for 48 hours at room temperature before study. The lungs we have studied came from children dying of natural causes. Necropsies were performed within 24 hours and the injection performed as part of this on the fresh lung.

Hislop and Reid used a concentrated solution of gelatin (25%) whereas we used a relatively weak concentration (2%). Their solution would be viscous necessitating the high injection pressures used (at least 10 kPa or 100 cm H_2O). Injection of a highly viscous solution at this unphysiological pressure appears likely to severely distort if not destroy small pulmonary arteries and arterioles. The assessment of the vessels in their work was predominantly on the study of radiographs. The only histology performed was the tracing of an axial pathway by serial section in which side branches were noted but not followed.

The conclusions we have reached are based on the measurement of pressures required to obtain free venous flow, and the measurement of particles able to pass through the pulmonary vascular bed. The histological observation of gelatin in the pulmonary veins confirms the findings seen during the injection. The resistance to flow through these vessels will be several thousand times lower than that of a

capillary (about 2000 for a diameter of 40 μm and 10 000 for a diameter of 60 μm based on the resistance being proportional to $1/r^4$).

The origin of these shunting vessels is of interest. It has been suggested that in the developing fetus there is a 'deep circulation' of blood in the lung which bypasses the capillary bed (M Rosan, personal communication). Two origins can thus be proposed for the origin of these shunting vessels: firstly that they are the remnants of this hypothetical 'deep' fetal circulation, or that they are an abnormality of development. The difficulty experienced in tracing the vessels from artery to vein suggests that shunt vessels are dispersed widely throughout the lungs with perhaps one or two in each lobule.

In conclusion we have confirmed the suggestion of Lauweryns (M Rosan, personal communication) that there is a 'deep' direct arteriovenous pathway bypassing the alveolar capillary bed in the lung. In some infants, under ill defined conditions, sudden opening of these shunt vessels could produce a large and possibly life threatening intrapulmonary shunt. While we continue to study these vessels histologically, physiological studies will be required to isolate the events which control their opening.

We are indebted to HM Coroners of Nottingham and Lincoln for access to the material, and to the coroner's officers and many members of the constabularies for their detailed records of the incidents.

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Role of aortopexy in the management of primary tracheomalacia and tracheobronchomalacia

P S Malone, E M Kiely

Abstract

Between 1986 and 1988 aortopexy was carried out on 12 patients with primary tracheomalacia and five with tracheobronchomalacia; their median age was 5 months (1 month–7 years). All patients had stridor, 14 had had cyanotic and apnoeic episodes, and 10 had had 'death' attacks. Eight patients (47%) had associated gastro-oesophageal reflux. Six patients (35%) were helped by aortopexy alone, and a further five (29%) improved with a combination of aortopexy and antireflux treatment. Four patients required tracheostomy, one of whom died. Aortopexy failed if gastro-oesophageal reflux was present. We recommend aggressive treatment of reflux combined with aortopexy in patients with primary tracheomalacia and tracheobronchomalacia.

Tracheomalacia is characterised by an abnormally soft and easily collapsible trachea. It often occurs in association with oesophageal atresia and tracheo-oesophageal fistula, but there is a less common primary form in which the bronchi as well as the trachea may be affected. It causes airway obstruction, particularly at times of high air flow such as when coughing, crying, and feeding. The typical symptom is stridor, which inevitably has an expiratory component. Severe forms produce repeated apnoeic and cyanotic episodes that can progress to 'death' attacks when bradycardia supervenes. Mild cases usually resolve spontaneously at about 1 year of age. In the more severe forms treatment is required to save life.

In the past, treatment consisted of long term intubation and ventilation or tracheostomy, but recently aortopexy has gained favour. Aortopexy entails suturing the anterior wall of the ascending aorta to the posterior surface of the sternum, which in turn pulls the anterior wall of the trachea forward and prevents collapse. Its initial success in the treatment of tracheomalacia associated with oesophageal atresia has encouraged surgeons to use it for the more uncommon primary tracheomalacia and tracheobronchomalacia.¹⁻³ To our knowledge there has been no previous study reporting the results of aortopexy in primary tracheomalacia, but the results in tracheobronchomalacia are disappointing.⁴ In 1987 we reported the results of aortopexy in 22 patients with oesophageal atresia.³ Using these as historical controls, we analysed our results of aortopexy in the management of primary tracheomalacia and tracheobronchomalacia.

Patients and methods

The records of all patients with a diagnosis of primary tracheomalacia or tracheobronchomalacia who underwent aortopexy between 1986 and 1988 were reviewed retrospectively. All patients were referred either from the respiratory or ear, nose, and throat departments of the hospital. In each case symptoms were typical of upper airway obstruction with nothing to suggest primary pulmonary disease. Pulmonary function studies were not carried out routinely.

There were 17 patients: 13 boys and four girls. Ages ranged from 1 month–7 years (median 5 months); symptoms are listed in table 1. 'Death' attacks are defined as the development of bradycardia, pallor, and floppiness after a prolonged apnoeic or cyanotic episode. Five patients with death attacks required full cardiopulmonary resuscitation and admission to an intensive care unit. The remaining five patients were given mouth to mouth resuscitation, and one required emergency tracheostomy on admission to hospital. Prolonged hypoxia secondary to a death attack was the only aetiological factor in both patients with cerebral palsy. All patients presenting with apnoeic or cyanotic episodes had further attacks in hospital before operation. Thirteen patients were symptomatic within the neonatal period, seven having had problems since birth. Three developed symptoms between 1 and 6 months of age, and one patient was over 6 months old. Associated features are listed in table 2. The patient who presented at 7 years of age had had an emergency tracheostomy performed at another unit when she was 3 years old. Numerous

Table 1 Symptoms in 12 patients with tracheomalacia and five with tracheobronchomalacia

Symptoms	No of patients
Stridor	17
Cyanotic or apnoeic attacks	14
'Death' attacks	10
Recurrent respiratory infections	3

Table 2 Associated features in 12 patients with tracheomalacia and five with tracheobronchomalacia

Feature	No of patients
Gastro-oesophageal reflux	8*
Prematurity (28, 32, and 35 weeks' gestation)	3
Cerebral palsy	2
Subglottic oedema or stenosis from prolonged intubation	2
Tracheostomy	1

*One patient had had a fundoplication, and did not have signs of reflux at aortopexy.

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Table 3 Extent of disease in 12 patients with tracheomalacia and five with tracheobronchomalacia

	No of patients
Tracheomalacia:	
Upper third trachea	0
Middle third trachea	2
Lower third trachea	8
Lower two thirds trachea	2
Tracheobronchomalacia:	
Lower two thirds trachea, both main bronchi	2
Lower two thirds trachea, left main bronchus	1
Lower third trachea, both main bronchi	1
Lower third trachea, right main bronchus	1

attempts at decannulation had failed, and she still had an isolated segment of tracheomalacia.

The diagnosis was always confirmed by bronchoscopy. Complete or almost complete occlusion of the airway was seen during quiet respiration in each case. Specific radiological views of the airways were also taken, but these were not helpful. The radiological investigation of most value was dynamic screening of the airways. Using the information provided by these investigations, the extent of tracheomalacia or tracheobronchomalacia could be defined (table 3).

Aortopexy was performed as previously described.^{3,5}

Results

There were no early deaths. One patient had a respiratory arrest within hours of operation and required intubation and ventilation for a short period. The most common postoperative complication was respiratory tract infection, and one patient developed a wound haematoma.

Six patients (35%) were cured with permanent relief of symptoms, and one (6%) was improved. Aortopexy failed to relieve symptoms in 10 patients (59%). Two patients underwent repeat aortopexy and tracheopexy, but these were not successful. Six patients in whom aortopexy failed had severe gastro-oesophageal reflux, which was confirmed by subsequent investigation. Four had a Nissen fundoplication, three of whom improved, and one of two patients who were treated medically also improved. This left six of the initial 17 patients in whom there was no symptomatic improvement. Four required tracheostomy, and only two have been successfully decannulated (one requiring a rib graft). One is awaiting decannulation and a patient with cerebral palsy who had a tracheostomy died from repeated chest infections at his local hospital. The patient who had a tracheostomy before aortopexy was not decannulated two years later because she was lost to follow up. Symptoms in the remaining patient were not severe enough to require tracheostomy but he had needed repeated hospital admissions for recurrent chest infections. Tracheobronchomalacia was not associated with failure; three of the five patients improved after aortopexy, with or without an additional Nissen fundoplication.

Discussion

Our results after aortopexy in this series con-

trast with our previously reported success in patients with tracheomalacia associated with oesophageal atresia and tracheo-oesophageal fistulas.³ In that series 19 of 22 patients (86%) were considerably improved after aortopexy, but only seven of 17 patients (41%) benefited in the present study. Three of the five patients with tracheobronchomalacia improved, suggesting that the inclusion of these patients was not the cause of the disappointing results. The 12 patients with tracheomalacia had disease in an isolated segment and no patient had a completely diseased intrathoracic trachea, a feature known to have a poor prognosis.^{1,2} It is, therefore, difficult to explain the failure of aortopexy in primary tracheomalacia.

We emphasise the association between primary tracheomalacia and gastro-oesophageal reflux, particularly in those patients for whom aortopexy failed. Blair *et al* reported similar findings in 1986, and we agree that it is sometimes difficult to determine whether it is the tracheomalacia or the reflux that is responsible for the clinical picture.² At present we rely on our bronchoscopic findings when deciding which condition takes priority, but it is possible in the future that the finding of reflux during sleep on 24 hour pH monitoring will identify this as the principle disease, and thus influence treatment.⁶ As our results now suggest that both conditions may need treatment, however, we advocate aggressive investigation and treatment of both the gastro-oesophageal reflux and the tracheomalacia.

As tracheomalacia is a self limiting condition that usually resolves spontaneously as the trachea stiffens, less aggressive forms of treatment have been advocated, including prolonged intubation and continuous positive airway pressure.^{7,8} The main disadvantage of this is that patients must stay in hospital for periods of a year or more. Prolonged intubation may cause subglottic oedema or stenosis (as occurred in two of our patients), a complication that has its own morbidity and mortality. The application of continuous positive airway pressure by nasopharyngeal prong also requires care in hospital, and we have found in a limited number of patients that it does not reliably prevent airway collapse. We therefore believe that some more definitive form of treatment is required.

Tracheostomy should be avoided as a primary procedure and used only as a last resort.^{1,9} It can cause secondary tracheomalacia, tracheal fibrosis, and formation of granulation tissue. In this study five patients had tracheostomies, but only one was carried out as a primary procedure (at another hospital). The other four were undertaken after aortopexy had failed. One of these patients (who had severe cerebral palsy) died when continued treatment was not considered justified. Of the remaining three patients, two have been decannulated and are alive and well, and one is awaiting decannulation. The patient with the primary tracheostomy who was lost to follow up after aortopexy is only now being assessed for decannulation.

Based on this experience our recommendations are as follows. All patients with suspected tracheomalacia should have the diagnosis con-

firmed by bronchoscopy. Gastro-oesophageal reflux should always be sought by barium studies, 24 hour pH monitoring, and oesophagoscopy. At the present time we recommend early aortopexy for those with severe symptoms, but in the future—with the widespread use of 24 hour pH monitoring—it may be possible to select those patients who would benefit from antireflux treatment alone. In patients with gastro-oesophageal reflux in whom aortopexy fails a Nissen fundoplication should be undertaken without delay. If this combined approach fails, tracheostomy is required.

We thank Mr CM Bailey, consultant ear, nose, and throat surgeon, and Dr R Dinwiddie and Dr D Matthew, consultant paediatricians, for referring these patients.

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Response to treatment of congenital adrenal hyperplasia in infancy

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Abstract

Nine infants with congenital adrenal hyperplasia were started on replacement doses of hydrocortisone (20.6–32.6 mg/m²/day) without receiving a high dose for an initial period first. Plasma adrenal steroid concentrations fell to acceptable levels by 3 months of age. Adequate biochemical control was maintained and satisfactory growth achieved even though the mean dose of hydrocortisone had been reduced to 15 mg/m²/day by the age of 3 years. Inadvertent overtreatment and growth suppression in infants with congenital adrenal hyperplasia may be avoided by using replacement doses from the start, and by permitting the relative dose of hydrocortisone to fall as the body surface area increases during the first years of life.

dose of steroid during the intercurrent illness characteristic of infancy and early childhood lead to adverse effects unless it is monitored closely.

In this paper we report a prospective study of longitudinal growth and changes in plasma adrenal steroid concentrations in nine infants with congenital adrenal hyperplasia. All received hydrocortisone after birth in replacement doses, adjusted during the subsequent years of life according to frequent measurements of plasma adrenal steroid concentrations. The results indicate that an initial period of high doses of glucocorticoid is unnecessary; a subsequent maintenance dose of hydrocortisone that permits minimally acceptable concentrations of plasma adrenal steroid can be needed to prevent growth suppression in infancy and early childhood.

The treatment of congenital adrenal hyperplasia in infancy and childhood usually results in reduced adult height.¹ Inadvertent overtreatment with glucocorticoids (particularly during infancy) and failure of catch up growth despite subsequent reduction of the dose of steroids are important contributors.² Several aspects of conventional management have led to overtreatment. Treatment was started with high doses of glucocorticoid to achieve rapid control, the dose then being reduced to maintenance replacement doses. The early recommended doses of glucocorticoids, which were based on urinary steroid excretion rates, were excessive. Those calculated according to the known rate of endogenous cortisol production, provide a general framework for adequate treatment, but individual patients can vary in their requirements for glucocorticoid replacement.^{3, 4} The use of urinary steroid excretion rates and single, random measurements of plasma adrenal androgen concentrations are not sensitive enough to detect glucocorticoid overdosage if there are no clinical signs.⁵ The practice of increasing the

Patients and methods

The diagnosis of congenital adrenal hyperplasia in nine patients (seven with classical salt wasting 21-hydroxylase deficiency, and two with simple virilising 11 β -hydroxylase deficiency) was established soon after birth (table). 21-Hydroxylase deficiency was confirmed by increased plasma 17OH-progesterone concentrations, which were measured in one or more samples collected before treatment was started. The diagnosis of 11 β -hydroxylase deficiency was based on plasma concentrations of 11-deoxycortisol and increased urinary excretion of its metabolite tetrahydro-11-deoxycortisol. Plasma testosterone concentrations were also raised in the patients in whom the steroid was measured before treatment.

Two patients (cases 5 and 7) each of whom had a salt losing crisis, initially required intravenous therapy and a single bolus dose of hydrocortisone. Oral glucocorticoid treatment was started within 1–47 days (mean 14 days) of presentation, and was given as hydrocortisone

Clinical details of infants with congenital adrenal hyperplasia and maximum steroid concentrations at diagnosis

Case No	Sex	Presentation	Age at diagnosis	Enzyme deficiency	Maximum 17OH-progesterone concentration (nmol/l)	Maximum testosterone concentration (nmol/l)
1	M	Prenatal diagnosis	16 weeks' gestation	21-hydroxylase	>380	>26.0
2	M	Failure to thrive	5 weeks	21-hydroxylase	>760	>26.0
3	M	Diarrhoea vomiting	2 weeks	21-hydroxylase	>380	Not measured
4	F	Ambiguous genitalia	2 weeks	21-hydroxylase	670	11.2
5	M	Failure to thrive	17 days	21-hydroxylase	1430	18.0
6	F	Ambiguous genitalia	1 day	21-hydroxylase	197	Not measured
7	M	Failure to thrive	1 month	21-hydroxylase	780	Not measured
8	F	Ambiguous genitalia	1 day	11 β -hydroxylase	1870*	22.0
9	F	Ambiguous genitalia	4 days	11 β -hydroxylase	>2000*	7.7

*=11-Deoxycortisol (nmol/l); >=concentrations above the upper limit of assay available at that time.

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in three divided doses, the total dose being 20.6–32.6 mg/m²/day (mean 25.7). Patients with 21-hydroxylase deficiency were also given fludrocortisone 0.1–0.15 mg/day.

Concentrations of testosterone, 17OH-progesterone, and 11-deoxycortisol where appropriate, were measured serially in blood samples collected between 0900–1100 at clinic visits every three months for up to three years after the start of treatment. Supine length (and later standing height) and weight were measured at each visit by a single trained observer. Growth velocity was calculated over six month intervals during the first year, and subsequently over periods of one year. Surface area was calculated from the height and weight according to standard nomograms.

Plasma concentrations of 17OH-progesterone,⁶ testosterone,⁷ and 11-deoxycortisol⁸ were measured using previously published methods.

Results

PLASMA 17OH-PROGESTERONE CONCENTRATIONS

The table and fig 1 show plasma 17OH-proges-

terone concentrations before and during the first month of treatment with hydrocortisone. The concentrations of 17OH-progesterone before treatment were high, a maximum of 1430 nmol/l being recorded. The concentrations of 17OH-progesterone in infants with 21-hydroxylase deficiency at some time before treatment were far higher than those found in normal or sick preterm infants, but values fluctuated from day to day to as low as 31 nmol/l.⁹ Those infants from whom several samples were taken during a single day showed no diurnal rhythm in 17OH-progesterone concentrations, but on one occasion there was a fall from 1430 to 273 nmol/l over a two hour period. 17OH-Progesterone concentrations in the two siblings with 11 β -hydroxylase deficiency were only slightly increased.

The pattern of plasma 17OH-progesterone concentrations during the first two years of life is shown in fig 2. By 3 months of age acceptable concentrations (median 84.1, interquartile range 11.3–90 nmol/l) of 17OH-progesterone had been achieved. There was a continued fall over the next two years without an increase in the daily dose of glucocorticoid.

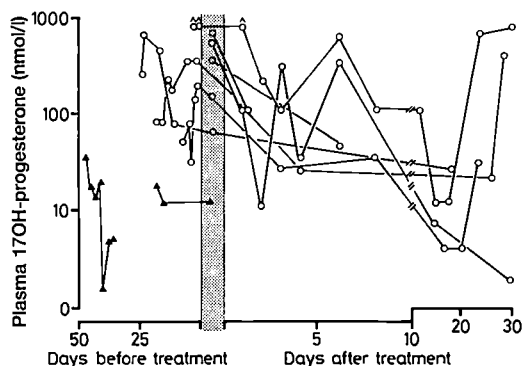


Figure 1 Plasma 17OH-progesterone concentrations in infants with congenital adrenal hyperplasia before and during first month of treatment with hydrocortisone. Shaded bar indicates start of treatment. (○=21-hydroxylase deficiency (n=7); ▲=11 β -hydroxylase deficiency (n=2).

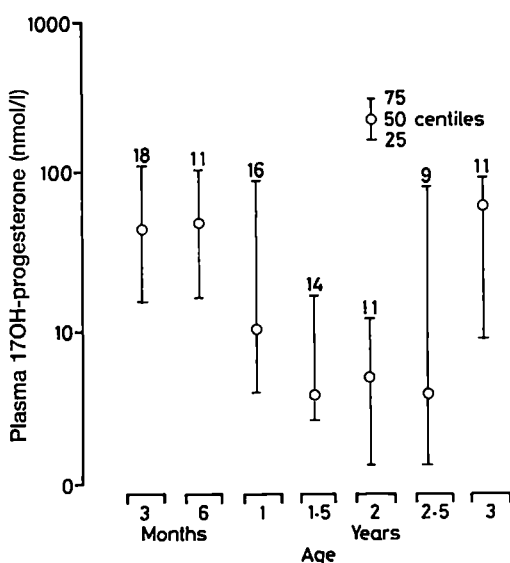


Figure 2 Plasma 17OH-progesterone concentrations achieved at various ages in infants with treated 21 hydroxylase deficiency (n=7). Centile values are derived from multiple measurements (number shown above bars) taken within one month of indicated age.

PLASMA TESTOSTERONE CONCENTRATIONS

Plasma testosterone concentrations were measured before treatment in six patients (table), and in both 21-hydroxylase deficiency and 11 β -hydroxylase deficiency they were considerably increased; they were within the normal range for adult men in all but one patient. Figure 3 shows the pattern of plasma testosterone concentrations during the early years of treatment. By the age of 3 months plasma testosterone concentrations had not yet come within the normal prepubertal range; those in male infants were slightly higher, consistent with the known increase in testicular testosterone production at this age.¹⁰

The plasma concentration of the specific marker for 11 β -hydroxylase deficiency, 11-deoxycortisol, was considerably increased in both siblings at diagnosis (table).¹¹ Concentrations of this steroid fell towards normal after three months of treatment (unpublished observations).

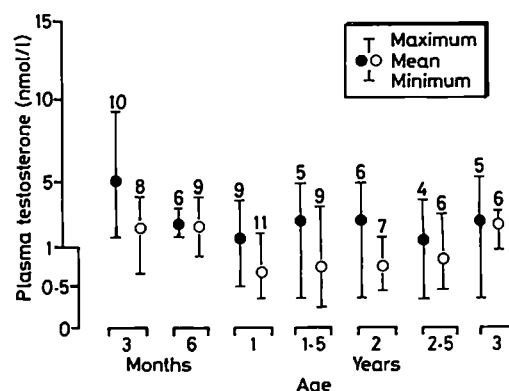


Figure 3 Plasma testosterone concentrations achieved at various ages in infants with treated congenital adrenal hyperplasia of all types (●=boys, n=5; ○=girls, n=4). Means and ranges are derived from multiple measurements (number shown above bars) taken within one month of indicated age.

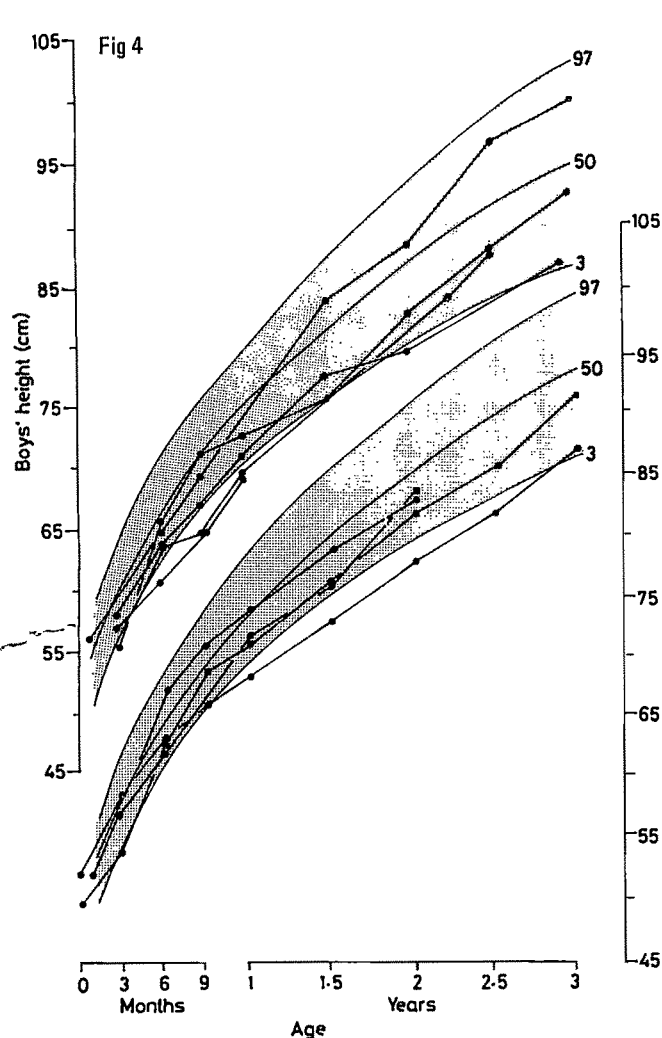


Figure 4 Height/length distance charts showing longitudinal growth data for nine infants (five boys, four girls) with treated congenital adrenal hyperplasia; 3, 50, and 97 indicate the respective centile lines.

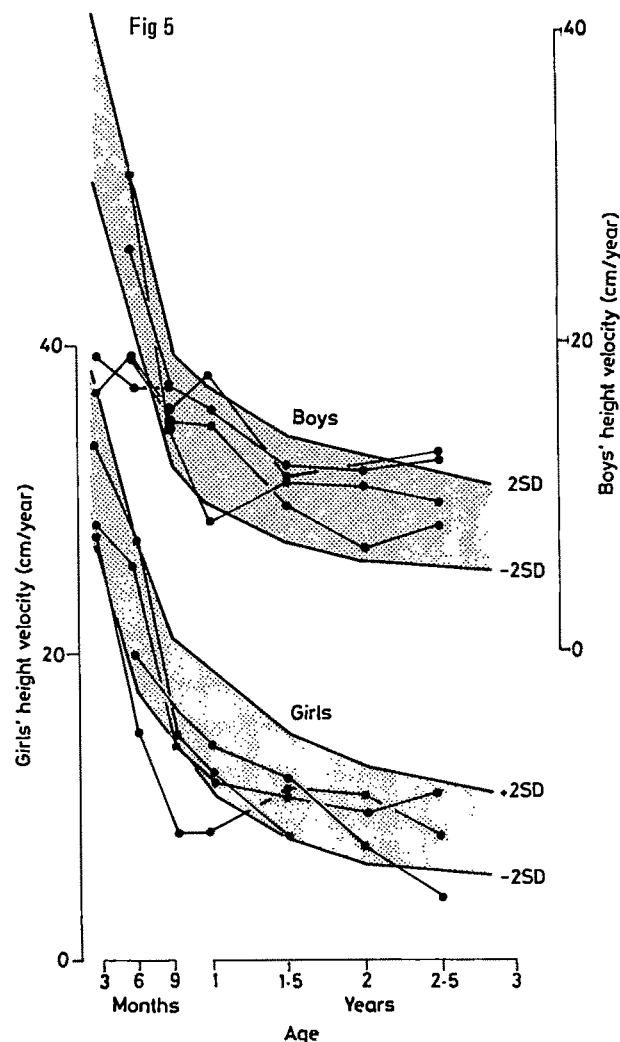


Figure 5 Growth velocity in nine infants with treated congenital adrenal hyperplasia (five boys, four girls). The shaded area encompasses the mean (2 SD) velocity data adapted from values provided by Tanner et al.¹³

GROWTH

The growth patterns during infancy and early childhood are shown in figs 4 and 5. Growth was generally normal; a few patients showed evidence of slower growth at 1 year, but then showed catch up growth as the dose of glucocorticoid was allowed to decrease in relation to increasing surface area.

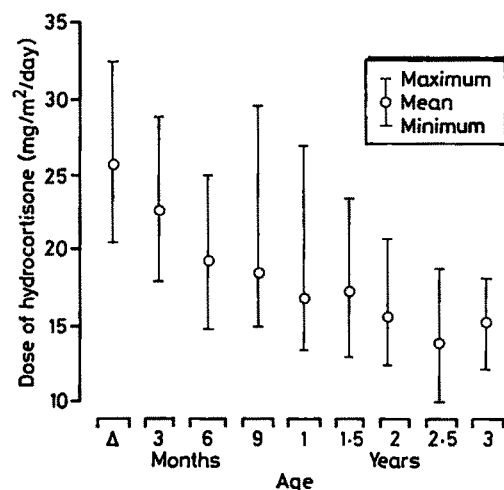


Figure 6 Doses of hydrocortisone achieved at various ages in nine infants with treated congenital adrenal hyperplasia; Δ indicates start of treatment.

TREATMENT WITH GLUCOCORTICOIDS

The changes in the dose of hydrocortisone with increasing age of the patients is shown in fig 6. There was a gradual decline from the mean starting dose ($25.7 \text{ mg/m}^2/\text{day}$, range $20.1\text{--}32.6$) as a result of using a fixed prescribed dose of hydrocortisone as each patients' surface area increased with growth.

Discussion

Measurement of the plasma 17OH-progesterone concentration is widely accepted as a reliable test for the diagnosis of 21-hydroxylase deficiency congenital adrenal hyperplasia.⁴ Maximum 17OH-progesterone concentrations in this study were clearly high compared with those of normal newborn infants. Wide fluctuations, however, resulted in some 17OH-progesterone values falling within the ranges found in sick premature infants without congenital adrenal hyperplasia.⁹ As a precaution, multiple estimations of 17OH-progesterone concentrations may be needed when investigating suspected congenital adrenal hyperplasia in newborn infants. Glucocorticoid treatment can usually be delayed until samples have been collected; the ability to measure 17OH-progesterone concentrations in blood spots or saliva eases the

difficulty of collecting multiple blood samples from infants.⁴

The clinical hallmark of congenital adrenal hyperplasia caused by both 21-hydroxylase and 11 β -hydroxylase deficiencies is virilisation in an affected girl. Plasma testosterone concentrations in all six infants studied were increased, and reached the normal range for adult men in two baby girls. Despite the profound androgenic influence that had existed prenatally, there was no evidence of masculinisation of the male external genitalia at birth, yet—if they had been left untreated—signs of masculinisation would have occurred during the second year of post-natal life. There is no ready explanation for this apparent development related onset of androgen responsiveness of the male genitalia. It used to be normal practice to start treatment with large doses of glucocorticoid, often administered parenterally, in order to achieve rapid suppression of adrenal androgen production.

The results of this study suggest that initial high dose treatment is unnecessary. Oral hydrocortisone (and fludrocortisone where appropriate) in replacement doses alone (hydrocortisone dose: mean 25.7 mg/m²/day, range 20.6–32.6; fludrocortisone 0.1–0.15 mg/day) produced rapid and sustained falls in plasma adrenal steroid concentrations without adverse clinical effects. Initial doses of hydrocortisone were within the range usually used for treatment of congenital adrenal hyperplasia at this time of life.^{2,4} Doses larger than this lead to early growth suppression. The slower growth rate at 1 year in some infants in this study suggests that perhaps the dose of hydrocortisone used was still slightly excessive. There was a subsequent improvement in growth when the dose was allowed to fall in relation to the increase in body surface area. Adult height in congenital adrenal hyperplasia remains below normal.¹ Infancy and early childhood are critical periods of rapid growth. The use of high doses of glucocorticoid from the onset of treatment may contribute to irreversible suppression of growth during the period.

We recommend starting hydrocortisone in replacement doses (20–25 mg/m²/day), equivalent to about 5 mg/day. A typical regimen in early infancy would be hydrocortisone 1.25, 1.25, and 2.5 mg given at intervals of eight

hours. It is necessary to formulate hydrocortisone in solution to calculate these small doses accurately. During the next two years the dose may be allowed to fall to as little as 10 mg/m²/day while the body surface area increases. Overzealous attempts to achieve normal plasma concentrations of 17OH-progesterone should be avoided as this invariably leads to gross over-treatment.⁵ The use of steroid profiles may help in preventing inadvertent overdosage in older infants with an established diurnal rhythm for plasma 17OH-progesterone.

Close observation of linear growth remains a key measure of control during the period of rapid growth in early infancy,¹² together with the use of biochemical monitoring to help with the adjustment of doses of steroid in the short term.

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Symptoms and transmission of intestinal cryptosporidiosis

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Abstract

Cryptosporidium spp are a cause of diarrhoea in toddlers. Symptoms and routes of transmission were investigated in a prospective case-control study in the city and surroundings of Basel, Switzerland. Twenty one (4.6%) out of 455 children with diarrhoea who attended paediatric and general practices from June to September 1988 were positive for cryptosporidium. The mothers of each case, of two controls with diarrhoea of another origin, and of two healthy controls were interviewed with a standardised questionnaire. In comparison with controls with diarrhoea of another origin, respiratory symptoms were significantly more frequent in children with cryptosporidiosis: eight of 19 (42%) compared with five of 38 (13%). In comparison with healthy controls, preceding contact with a person suffering from diarrhoea was associated with the greatest relative risk for cryptosporidiosis, followed by travel in a Mediterranean country. Transient cryptosporidial infection of the respiratory tract may be common in immunocompetent children. In the area investigated person to person transmission may account for most cases.

Cryptosporidium spp, a coccidian parasite first described in 1907,¹ has only recently been recognised as a relatively frequent cause of diarrhoea in children. In Switzerland 5.5% of children with diarrhoea identified by a laboratory based survey were found to be positive for oocysts of *Cryptosporidium* spp.² In immunocompetent children the disease is usually self limiting, but it may be severe in immunodeficient patients.²⁻³ Cryptosporidiosis has been considered as an 'emerging zoonosis' with reservoirs in cattle and domestic animals, and in the faecally contaminated environment.⁴ Other ways of transmission have been reported, including person to person transmission,⁵ and transmission by contaminated food and water—for example, when travelling.⁶ Outbreaks in daycare centres and families have been documented.⁷

In order to elucidate symptoms and major routes of transmission associated with this parasitosis in an urban and periurban area of Switzerland, the present case-control study was undertaken.

Patients and methods

Eleven paediatric and general practices in the city of Basel, Switzerland, and 29 practices in the periurban areas around Basel participated in

the study. All children up to the age of 16 who presented with diarrhoea at one of the practices during the period June to September 1988 were included in the study. At least two stool specimens from each child were subsequently examined for oocysts of *Cryptosporidium* spp using the auramine fluorescence staining technique.² In doubtful cases the stool samples were concentrated using the method according to Ritchie,⁸ and the modified Ziehl-Neelson staining technique was used for the sediment.⁹ All oocyst positive stools were examined for rotavirus and adenovirus using latex agglutination (Diarlex, Orion Diagnostica); for salmonella, shigella, yersinia, campylobacter using selective mediums (Bio Mérieux); and for *Giardia lamblia* and *Entamoeba histolytica* (MIF-concentration method¹⁰).

Cases were defined as all patients with diarrhoea with at least one oocyst positive stool and no concomitant infection with another agent.

Diarrhoea controls: for each case, two patients with diarrhoea who were negative for oocysts were randomly selected and frequency matched to cases for age. Age strata were as follows: <2 years, 2-4 years, 4-7 years, and >7 years.

Also for each case, two healthy control children were randomly selected from the children who had attended the study practices for various reasons but not for diarrhoea. They were selected as soon as diagnosis in the corresponding case had been made, and were matched to cases for sex and age within the same strata.

STANDARDISED INTERVIEW

Mothers of cases of cryptosporidiosis, of healthy controls, and of controls with other causes of diarrhoea were interviewed by two of us (DM and PO) using an identical questionnaire. Interviews in the case and in the healthy controls were carried out by the same person just after diagnosis of the case. The questionnaire consisted of 122 mainly closed questions. It had been tested for ambiguity and interobserver variation in a pilot study. Information was sought relating to personal medical history, living conditions, behavioural patterns, animal contact (including pets), contacts with persons suffering from diarrhoea, consumption of food and drink (quantity and type), and travelling. The questions covered the time period 10 days before the onset of disease in patients and 10 days preceding the interview in healthy controls. In children with cryptosporidiosis and controls with diarrhoea additional questions relating to symptoms and severity of disease were included.

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STATISTICAL ANALYSIS

Student's unpaired, two tailed *t* tests and χ^2 tests with continuity correction were used for the comparison of groups. Fisher's exact test was used if the smallest expected value was less than five. Two sided Fisher's exact tests were calculated taking the total probability of tables, in either tail, which were at least as small as the one observed.¹¹ A matched case-control analysis was performed.¹² Regression for conditional likelihood¹³ was used for the calculation of univariate relative risk estimates, 95% confidence intervals, and likelihood ratio (χ^2) statistics (program PECAN, version 2.1¹⁴).

Results

During the study period 455 children with diarrhoea were identified. Twenty one (4.6%) were positive for oocysts of *Cryptosporidium* spp (June 2.5%, July 0%, August 6.6%, September 6.8%). Two children were excluded from analysis because they were concomitantly infected with rotavirus or salmonella. Therefore, in the analysis 19 children with cryptosporidiosis were compared with 38 healthy controls and 38 controls suffering from diarrhoea of another origin. All study children were considered immunocompetent by their physician.

Three cases of cryptosporidiosis were part of a family outbreak. Another child had visited a kindergarten where nine out of 22 children and the two teachers were suffering from diarrhoea. These outbreaks will be reported elsewhere. The remaining 15 cryptosporidiosis cases could not be traced to an outbreak.

Table 1 shows the clinical characteristics of study patients. Age and sex were similar among cases and controls. Cryptosporidiosis cases more often lived in the city of Basel than in the periurban areas. Living conditions were not more crowded than those of control patients as judged by the number of persons per room.

Table 2 shows data relating to symptoms in cryptosporidiosis cases and age matched oocyst negative controls with diarrhoea. Fever was milder in cryptosporidiosis patients. Duration of diarrhoea, frequency of gastrointestinal symptoms, and stool characteristics were very similar in children with cryptosporidiosis and controls with diarrhoea. However, cough was noted in eight of 19 cryptosporidiosis cases (42%) compared with only five of 38 controls (13%) with diarrhoea ($p=0.02$). The relative risk for cough was 3.2 with a 95% confidence interval of 1.2 to 8.4.

Table 3 shows frequencies of exposure to possible sources of infection in cases of crypto-

Table 2 Severity of disease and symptoms in children with cryptosporidiosis and controls with diarrhoea of origin

	Children with cryptosporidiosis (n=19)	Controls with diarrhoea of another origin (n=38)	
Mean (SD) duration of diarrhoea (days)	9.8 (10)	13.1 (16)	0.05
No (%) with fever ($\geq 37.5^\circ\text{C}$)	11 (57)	23 (60)	0.5
Mean (SD) highest temperature measured ($^\circ\text{C}$)	38.0 (0.8)	38.6 (1.0)	0.5
No (%) with:			
Abdominal pain	13 (68)	28 (74)	0.5
Abdominal cramps	7 (37)	15 (39)	0.9
Vomiting	12 (63)	19 (50)	0.5
Meteorism	6 (31)	9 (24)	0.7
Stools:			
Watery	13 (69)	17 (46)	
Bloody	1 (5)	4 (10)	
Slimy	5 (26)	17 (44)	0.23
Cough	8 (42)	5 (13)	0.02†

*Student's *t* tests and χ^2 tests with continuity correction except for †two sided Fisher's exact test.

sporidiosis and healthy controls. Preceding contact with a person suffering from diarrhoea was mentioned in 10 of 19 cases (52%) but only in one of 38 controls (3%). Attendance at a kindergarten was also more frequent in cases. On the other hand, frequency of contact with any animal was not different in the two groups. There is evidence that preceding contact with a cat or dog, however, that failed to thrive was more frequent in children with cryptosporidiosis. Use of dummies and preceding holidays in the Mediterranean region (Spain, Southern Italy, Turkey, and Israel) were also more frequent among children with cryptosporidiosis. Consumption of various food items including salad vegetables was similar in the two groups except for unpasteurised milk, which was consumed by five of the 19 cases (26%) compared with three of the 38 controls (8%). Relative risk estimates and 95% confidence intervals, calculated by conditional logistic regression, are also shown. Contact with a person suffering from diarrhoea was associated with the greatest relative risk, followed by travel in a Mediterranean country. However, the importance of an exposure should not only be judged from the relative risk. The attributable risk takes the frequency of an exposure in the population into account and indicates the proportion of cases which may be attributable to an exposure.¹⁵ From this point of view person contact again ranked first (attributable risk: 33%), followed by animal contact (26%), consumption of unpasteurised milk (20%), and travelling to Mediterranean countries (16%).

Discussion

Cryptosporidiosis is a cause of acute, self limiting diarrhoea in immunocompetent toddlers but may lead to severe, life threatening diarrhoea if immunodeficiency is present.³ Patients with AIDS and patients treated with immunosuppressive drugs are at risk. In the absence of an effective treatment, prevention of cryptosporidial infection is essential. For that purpose the importance of different possible ways of transmission should be known. Whereas it is seldom possible to establish the chain of infection in

Table 1 Characteristics of children with cryptosporidiosis, controls with diarrhoea of another origin, and healthy controls

	Children with cryptosporidiosis (n=19)	Controls with diarrhoea of another origin (n=38)	Healthy controls (n=38)
Mean (SD) age (years)	5.4 (4)	4.7 (3)	5.4 (4)
Sex (M:F)	14:5	23:15	28:10
No (%) at place of residence:*			
Urban	7 (37)†	7 (18)	5 (13)†
Periurban	12 (63)	31 (82)	33 (87)
Mean (SD) No of persons/room	1.00 (0.3)	0.93 (0.2)	1.01 (0.3)

*Urban: Basel county city (Kanton Basel-Stadt); periurban: Basel county country (Kanton Basel-Land).

† $p=0.08$ for comparison healthy controls compared with cryptosporidiosis cases (two sided Fisher's exact test).

Table 3 Exposure frequencies among children with cryptosporidiosis and healthy controls and univariate relative risk estimates with 95% confidence intervals from logistic regression analysis. Results are numbers (%)

	Children with cryptosporidiosis (n=19)	Healthy controls (n=38)	p Value*	Relative risk	95% Confidence interval
Contact with person suffering from diarrhoea	10 (52)	1 (3)	<0.001†	20.0	2.5 to 156
Visited kindergarten	4 (21)	2 (5)	0.08†	4.0	0.73 to 22
Animal contact:					
Any	16 (84)	31 (82)	0.90	—	—
Dog	11 (58)	19 (50)	0.78	—	—
Cat	11 (58)	19 (50)	0.78	—	—
Calf	1 (5)	1 (3)	0.79	—	—
Dog, skinny	4 (21)	2 (5)	0.08†	4.0	0.73 to 22
Cat, skinny	4 (21)	2 (5)	0.08†	4.0	0.73 to 22
Dummy	10 (53)	12 (31)	0.21	3.2	0.80 to 12
Travelled in Mediterranean country	5 (26)	2 (5)	0.03†	5.0	1.1 to 25
Consumed untreated milk	5 (26)	3 (8)	0.10†	4.3	0.85 to 22

* χ^2 tests with continuity correction except for †=two sided Fisher's exact test.

individual cases, case-control studies can identify the exposures which are associated with the disease.

In this study contact with a person suffering from diarrhoea was the most important risk factor for intestinal cryptosporidiosis in children living in an urban and periurban area in Switzerland. A weak association with cats and dogs who were failing to thrive but not with healthy animals was evident. These results indicate that most cases were infected by person to person transmission. Consumption of untreated milk may also be a risk factor and may be an important source of infection in rural areas. Pasteurisation destroys infective oocysts.¹⁶ Our results also suggest that *Cryptosporidium* spp may be a cause of traveller's diarrhoea.⁶ Dummies were also associated with the disease and because of their widespread use they and other fomites may often play an important part in the chain of infection. This finding is not surprising in the light of the high degree of environmental resistance of cryptosporidial oocysts.¹⁷

Concomitant bronchitis was significantly more frequent in cases of cryptosporidiosis than in age matched children suffering from diarrhoea of different origin. Respiratory cryptosporidiosis is an established complication in AIDS patients.¹⁸ Harari *et al.*, however, also detected oocysts in the tracheal fluid of an immunocompetent child, aged 8 months, who was suffering from severe bronchitis and gastroenteritis.¹⁹ In addition, respiratory symptoms were mentioned in two case series from Bangladesh and Brazil where six out of 18 (33%) and five out of nine (55%) immunocompetent cases were affected with bronchitis.^{20, 21} Our results suggest that transitory cryptosporidial infection of the respiratory tract may be common in immunocompetent children. This infection may be acquired by inhaled oocysts or by small aspirates of vomit that contains oocysts.²² Further studies are still needed in order to investigate the importance of respiratory infections with *Cryptosporidium* spp in immunocompetent children.

Cats and dogs who fail to thrive may well be suffering from chronic cryptosporidiosis²³ and transmit the disease to humans and especially children.²⁴ Despite this fact, our findings suggest that person to person transmission is the major route of infection in our urban and periurban setting. The findings of this controlled study therefore support the hypothesis put forward by Casemore and Jackson, that

'cryptosporidiosis should not be regarded primarily as a zoonosis'.²⁵

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Treatment of constitutional delay of growth and puberty with oxandrolone compared with growth hormone

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Abstract

The effects of oxandrolone or biosynthetic human growth hormone (r-hGH) on the growth of 26 boys with constitutional delay of growth and puberty were studied. Both regimens increased growth rate twofold, oxandrolone to a greater extent than r-hGH. We conclude that oxandrolone is a more effective method of increasing growth rate in such children.

Constitutional delay of growth and puberty occurs in healthy adolescents whose height is reduced for chronological age but generally appropriate for bone age and the stage of pubertal development, both of which are usually delayed. Anabolic steroids, given in low doses, produce an acceleration in growth rate that is maintained when treatment is stopped, provided that the testicular volume is over 5 ml.¹⁻³ Eventual height does not seem to be increased, but perhaps more importantly it is not compromised.¹ Transient growth hormone insufficiency is a feature of constitutional delay of growth and puberty⁴ so growth hormone might be a more effective treatment in terms of eventual height.⁵

We have investigated the role of oxandrolone and growth hormone on the growth of 26 adolescents with constitutional delay of growth and puberty and compared the results at the end of one year.

Patients and methods

Twenty six boys with constitutional delay of growth and puberty (mean age 13.8 years) were randomly allocated to receive oxandrolone (Searle) in a dose of 2.5 mg orally at night for three months (n=15) or biosynthetic human growth hormone (r-hGH) (Genotropin, Kabi) in a dose of 20 units/m²/week (nightly subcutaneous injections) for one year (n=11). The patients were observed for one year before treatment and followed up for a further year. The oxandrolone group therefore received treatment for three

months and had no treatment for nine months, whereas the r-hGH group had treatment for 12 months. The after treatment auxological data refer to measures made at the end of this 12 month period in both groups.

Standard anthropometric measurements were made at intervals of three months and bone age assessed before and after the follow up period. Pubertal staging was recorded at each clinic visit using the method of Tanner.⁶ The studies were approved by the Middlesex Hospital ethics committee, and informed consent was obtained. All data were expressed as standard deviation scores (SD scores) and results analysed by the Wilcoxon signed rank sum test and Mann-Whitney U test.

Results

The anthropometric measurements at the start of treatment and at the end of the subsequent year are shown in the table. All children fulfilled the criteria for the diagnosis of constitutional delay of growth and puberty with delayed bone age, normal height SD score for bone age, and delayed pubertal development. There were no significant differences between the groups before treatment (Mann-Whitney $p>0.05$).

Both treatments resulted in significant increases in height velocity, from a pretreatment median value of 3.9 cm/year to 8.3 cm/year for the oxandrolone treated group (Wilcoxon $p=0.01$), and from 3.8 cm/year to 6.8 cm/year for the r-hGH treated group (Wilcoxon, $p=0.01$). The increment in height velocity induced by oxandrolone was significantly greater than that induced by growth hormone (median oxandrolone 4.4 cm/year; median r-hGH 3.0 cm/year; Mann-Whitney $p=0.02$). Pubertal advance was similar in both groups as shown by their similar testicular volumes at the end of the year.

Discussion

Growth delay associated with delayed puberty is

Anthropometric data of 26 adolescent boys—values are given as median (range)

Measurement	Before treatment		After treatment	
	Oxandrolone	Growth hormone	Oxandrolone	Growth hormone
Chronological age (years)	13.8 (12.1-15.4)	13.9 (12.1-15.9)	14.8 (12.0-16.6)	15.0 (12.2-16.9)
Testicular volume (ml)	5.8 (3.0-8.0)	4.8 (2.0-8.0)	10.0 (6.0-15.0)	10.7 (6.0-15.0)
Height velocity (cm/year)	3.9 (2.6-5.3)	3.8 (2.0-5.3)	8.3 (6.3-11.1)	6.8 (5.1-9.0)
Height velocity increment (cm/year/year)			4.4 (1.3-8.1)	3.0 (1.5-5.1)
Bone age delay (years)	-2.1 (-4.3 to -0.2)	-2.3 (-5.1 to -1.0)	-2.2 (-4.2 to -0.4)	-3.0 (-4.7 to -1.2)
Height SD score for bone age	-0.8 (-2.2 to +1.2)	-0.6 (-2.9 to +1.2)	-0.2 (-2.2 to +1.3)	-0.1 (-1.4 to +1.5)

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common in boys and may cause deviant behaviour and severe psychological problems. Most of these boys do not require extensive endocrinological investigations, which may be misleading as a result of transient growth hormone insufficiency, but they do urgently need treatment for their delay in growth and puberty.⁴ Both oxandrolone and growth hormone produced acceleration of growth in boys with constitutional delay of growth and puberty without any difference in testicular volumes.

This increased height velocity is not a placebo effect² nor can it be attributed to the boys' own spontaneous growth spurt, as this does not occur until a testicular volume of 12 ml is reached.⁶ Only three of the boys receiving oxandrolone and two of those receiving r-hGH had testicular volumes of 12 ml or more at the end of the year of follow up. The significant difference in height velocity increment between oxandrolone and growth hormone could be the result of the sustained effect of oxandrolone previously noted.¹⁻³ It is certainly not that oxandrolone triggers the pubertal growth spurt, as both groups had similar testicular volumes of (10 ml) at the end of the study. There was therefore no difference in the speed of the

progression through puberty between the two groups.

We consider that growth hormone is not indicated for the management of delay in the onset of the pubertal component of the human growth curve, but whether longer periods of treatment (more than one year) with growth hormone in constitutional delay of growth and puberty would increase eventual height is still in question.

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Endotracheal compared with intravenous administration of atropine

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Abstract

Endotracheal and intravenous administration of atropine were compared in two groups of 10 children. No differences were found between the groups in effect on heart rate or speed of onset of the effect. We conclude that the two methods are equally effective.

Giving drugs by the endotracheal route has been recommended for use in resuscitation when venous access is not immediately available.¹ Atropine, adrenaline, and lignocaine have all been given in this way.²⁻³ Most of the supporting data come from animal studies, but recently doubt has been expressed about the plasma concentrations achieved in adults after drugs have been given by the endotracheal route.⁴ We therefore investigated the effect of atropine given in this way to children, measuring changes in the heart rate after a bolus dose.

Patients and methods

Twenty children aged between 1 and 8 years undergoing routine anaesthesia that required endotracheal intubation and neuromuscular blockade (for peripheral orthopaedic or urological operations) were studied. Informed

consent was obtained and the children were randomly allocated to receive either atropine 25 µg/kg (diluted to 2 ml with 0.9% saline) intravenously and 2 ml 0.9% saline endotracheally, simultaneously, or atropine 50 µg/kg (diluted to 2 ml with 0.9% saline) endotracheally and 2 ml 0.9% saline intravenously, simultaneously. Neostigmine (50 µg/kg) was given six minutes later to reverse the effect of the neuromuscular blockage.

Heart rate was monitored continuously using an electrocardiograph (Simonsen and Weel DS521) and recorded on a two channel paper chart recorder for 12 minutes after the atropine had been given. The endotracheal solution was given with a standard 2 ml syringe without adaptation and was followed by five manual hyperinflations of the chest. The intravenous solution was given through an indwelling cannula in the hand or arm.

Table 1 Comparability of the groups. Values are expressed as mean (SEM) except where otherwise stated

	Intravenous group (n=10)	Endotracheal group (n=10)
F:M ratio	4:6	5:5
Age (years)	4 (0.8)	3.4 (0.9)
Weight (kg)	15.8 (2.3)	15.4 (2.5)

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Table 2 Analysis of heart rate changes and time to maximum heart rate changes. Values expressed as mean (SEM)

	Intravenous group (n=10)	Endotracheal group (n=10)	p Value
Baseline heart rate (bpm)	127.3 (9.0)	121.4 (9.6)	0.4
Maximum change in heart rate	36.7 (5.5)	31.3 (5.7)	0.5
Percentage maximum change in heart rate	30.2 (7.1)	32.8 (7.3)	0.8
Time to maximum change (secs)	135 (13.6)	165 (17.5)	0.2

The data were analysed by Student's *t* test, and a probability of <0.05 was accepted as significant.

Results

The groups were comparable for sex, age, and weight (table 1). For each patient the efficacy of the atropine was assessed by the increase in pulse rate, the percentage change from baseline, and the time taken for maximum effect. In none of these categories were the groups significantly different (table 2).

Discussion

Although the endotracheal route is recommended for giving some of the drugs used in resuscitation,¹ there is conflicting evidence about its efficacy.²⁻⁴ In this study, endotracheal atropine resulted in a tachycardia that was clinically and statistically indistinguishable from that found when the drug was given intravenously.

Because both groups were given endotracheal fluid we were concerned that any tachycardia associated with mechanical stimulation should not confuse that caused by the vagolytic effect of the atropine. We think that this was unlikely for three reasons. Firstly, the size and timing of the changes in heart rate were similar in both groups. If the tachycardia in the endotracheal group was solely the result of mechanical stimulation it would be shorter and less pronounced than in the intravenous group. Secondly, a small initial tachycardia was seen in both groups after the endotracheal fluid had been given. This was followed by a longer, sustained rise in heart rate. Thirdly, there was no bradycardia after the neostigmine had been given to reverse the muscle relaxant six minutes later.

The method of administration was designed to simulate that most likely to be used in an emergency. The drug was given directly from a plain syringe, and five manual inflations of the chest were carried out to disperse it. We used the dose recommended by the Resuscitation Council, which is twice the normal intravenous

dose. Delivery of the drug from the tip of the endotracheal tube using a catheter has been described in most previous reports.³⁻⁶ Although more reliable delivery of the total dose of the drug is likely to be achieved, we felt that this method was unlikely to be used in an emergency.

A number of previous studies have examined blood concentrations of drugs after endotracheal administration. In animal studies low initial plasma concentrations with prolonged duration of action have been found, and it has been suggested that a reservoir effect in the lung may explain this.⁵

The blood concentration achieved will also be influenced by several other factors, including the dose, dilution volume, and cardiac output. All our patients had normal cardiac function, whereas during resuscitation cardiac output is likely to be low. In dogs after cardiac arrest² or with hypoxia induced bradycardia⁶ the endotracheal route was found to be as effective as the intravenous route. Conversely, in adults after cardiac arrest, low blood concentrations were found after adrenaline was given endotracheally, although the same dose was used for both the intravenous and endotracheal routes.⁴

It is not possible to predict the effect of low cardiac output on absorption from the lungs from our study, and further work is required.

In conclusion, 50 µg/kg (diluted to 2 ml) of atropine given endotracheally is as effective as 25 µg/kg given intravenously in children with normal cardiac function.

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Five year outcome of preterm sextuplets related to size at birth

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Abstract

Preterm sextuplets were studied to examine whether growth retardation affects long term outcome. All were growing normally at 5 years. Intelligence quotients (IQ) ranged from 105–116 and motor impairment scores from 1.0–7.0. No neurological or behavioural abnormalities were found. The largest sextuplet has maintained her position for growth and IQ. No relation between test scores and birth weight or perinatal variables was found in the remaining siblings.

Although severe intrauterine growth retardation is associated with a high mortality and long term morbidity, the degree to which lesser degrees of growth retardation cause problems is uncertain. One possible reason for the differences of opinion is the presence of many factors other than gestation that seem to affect fetal size at birth.¹ The arbitrary use of the 10th centile of weight for gestational age to separate those thought to be at risk is associated with a high false positive rate, because normal small subjects are included with those who have failed to reach their full potential. Comparison of the performance of children who are small for gestational age with those who weighed more at birth is also attended by many confounding variables in terms of parental size and associated socioenvironmental factors.¹

One way round these difficulties is to examine children from multiple pregnancies in which growth has been uneven. We report the five year neurodevelopmental outcome for sextuplets as an example of the effect of growth retardation when preconceptional and postnatal environment are the same.

Patients and methods

The pregnancy was conceived while the mother was being treated with follicle stimulating hormone and luteinising hormone (Pergonal, Serono) for primary infertility. Six fetuses were identified on the initial ultrasound scan. The mother was admitted to hospital in early

pregnancy and treated with ritodrine from 14 weeks. Preterm labour at 29 weeks' gestation stopped after ritodrine was given intravenously together with a course of betamethasone. At 31 weeks' gestation an urgent caesarean section was carried out because of increasing maternal oedema and discomfort. Six teams each comprising one doctor and two nurses attended the delivery. All the sextuplets were girls, and five of them required intubation and ventilation at birth. One subsequently required no ventilation, two were extubated by 4 hours of age, and the remaining three received mechanical ventilation for 14, 20, and 66 hours respectively, for hyaline membrane disease. Their subsequent progress was unremarkable, except that one child (case 4) had a serious apnoeic attack at 56 days, which required resuscitation and a course of antibiotics. Perinatal details are shown in table 1. The children were followed up prospectively at yearly intervals by one observer (RWIC). No serious illnesses or neurodevelopmental problems were encountered.

For the five year assessment all the siblings were examined on the same morning by observers who were unaware of the perinatal course or birth weights. The assessment comprised: a full neurological examination,² the test of motor impairment (NM),³ the British ability scales (AME), a Rutter A(2) parental questionnaire, and measurement of height, weight, and head circumference. Seven subscales of the British ability scales were used to compute a general quotient (IQ) with visual and verbal sub-quotients.⁴ The children were 62 months old at assessment.

Results

Each child completed all parts of the test. No child had a focal neurological abnormality. Four were right handed, one was uncertain (case 5), and one left handed (case 6). Four were observed to have two or more minor neurological signs. The impairment scores ranged from 1.0 to 7.0. The median score for a group of 53 control children at 6 years of age examined by the same observer was 3.0.⁵

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Table 1 Perinatal details of the sextuplets

Case No	Birth weight		Head circumference (cm)	Apgar score		First pH analysis	No of days ventilated	Blood group
	g	SD score*		1 min	5 min			
1	1598	-0.21	28.8	2	5	7.12	4	A
2	1340	-1.24	28.5	2	5	7.32	66	O†
3	1290	-1.44	27.7	5	9	7.18	4	O
4	1230	-1.68	27.4	3	8	7.17	20	O†
5	1060	-2.36	26.7	9	9	7.23	—	O†
6	930	-2.88	26.0	4	8	7.23	14	O

*SD score=difference from the mean for each age related measurement divided by the SD taken from normative data. †=similar, minor blood groups but different HLA types.

Table 2 Five year outcome measures

Case No	Height (cm)	Weight (kg)	Head circumference (cm)	British ability scales			Test of motor impairment score	No of minor neurological signs	Rutter behavioural score
				General IQ	Visual IQ	Verbal IQ			
1	124.0	24.6	52	116	117	116	3.5	0	4
2	111.5	17.6	50	106	110	106	1.0	3	18
3	117.0	18.5	50	108	100	108	7.0	3	17
4	111.5	17.6	50	110	103	110	6.5	3	11
5	112.5	16.0	48	105	106	105	6.0	0	10
6	114.5	17.2	49	110	107	109	2.0	2	14

IQ scores ranged from 105 to 116. One child (case 2) had a high verbal compared with visual score, and two (cases 3 and 4) had low visual scores. Both of these also had high impairment scores (6.5 and 7.0, respectively). The remaining results are shown in table 2.

The birth weights fell into three groups, and the occipitofrontal head circumference for each child corresponded to the birth weight. Two were more than 2 SD below the mean for 31 weeks' gestation, and three were between 1 and 2 SD. All were growing satisfactorily at 5 years: height SD scores ranged from +0.66 to +3.4. The child with the least deviation of birth weight from the mean (case 1) has maintained her position in terms of growth and IQ. She has blood group A. The remainder were blood group O, three with identical minor blood groupings but different HLA types. Among these five no relationship between birth weight and IQ, subscale, or impairment scores could be identified. No perinatal factor was able to predict the order of any outcome variable at 5 years.

Discussion

Many preconceptional and environmental factors determine birth weight, including maternal age, size, parity, and socioeconomic class. Among social factors smoking is perhaps the most important.¹ Such complex influences make the interpretation of studies of the influence of birth weight for gestational age on neurodevelopmental outcome difficult to interpret, as most do not control for such confounding genetic and environmental factors and none are prospective. Although there is evidence of disadvantage among small for gestational age children born at full term, those studies that attempt to study the outcome of preterm small for gestational age children are generally inconclusive.⁶

The chance to study a sibship of six who were exposed to the same preconceptional and rearing environments was therefore of great interest. None the less, even siblings in this sextuplet group have differing genetic influences,

as shown by the differences in blood group and HLA typing. The birth weights, which presumably reflect the degree to which each child achieved its growth potential, fall into three groups. The heaviest child at birth, with a different ABO group from her siblings, has maintained her position in terms of growth and five year IQ test scores. Among the three sextuplets whose birth weights fell between -1.0 and -2.0 SD below the mean there are no clear differences in growth or test scores compared with the two whose birth weights were more than 2 SD below the mean. Impairment scores, neurological signs, and behavioural scores were similarly unrelated to perinatal variables.

A similar range of tests was used to study the six year performance of 53 children with birth weights of less than 1251 g.⁵ Within this group no influence of birth weight or gestational age was found, but multiple regression analysis associated low five minute Apgar scores, neonatal neurological abnormality, and neonatal septicaemia, with poor impairment scores. None of the sextuplets had any neonatal neurological abnormality and all had normal cerebral ultrasound scans. Their test scores follow a similar pattern to our previous study, with normal IQs and a wide range of motor impairment scores.

In these sextuplets, therefore, though the largest at birth has maintained her position in terms of growth and IQ, no effect of birth weight or perinatal events was found among the remainder.

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PERSONAL PRACTICE

Treatment of epilepsy in people with multiple handicap

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Eight years ago, the writer visited a home for severely handicapped children, many of whom were epileptic. As it was school holidays, they were all in the hall of an old manor house used as a children's home. In an hour six of the 40 children had a fit, and six slept on, unrouseable. The experience was memorable.

Since then 51 very severely handicapped epileptic children age between 2 and 16 have been managed personally for at least two years. It has been surprising to see how the treatment pattern has changed over the years, and pleasant to see how few children are now having frequent fits, or are heavily sedated. These children are used as illustrations of the principles involved.

Multiply handicapped people are well known to have epilepsy that is difficult to treat,¹ especially severely brain damaged children, children with onset of fits in the first year of life, or children who have had infantile spasms or Lennox-Gastaut myoclonic fits.²⁻³ All the children described fall into at least one of these categories. Previous papers on epilepsy in people with multiple handicaps have been about adults.⁴⁻⁶ Controlling fits in 'normal' children with one drug can be surprisingly difficult,⁷ and in those with brain damage, it is likely to be even more difficult. However, it is still better to treat with one drug rather than a cocktail.⁸

Patients

The classification of patients by cause is shown in table 1. There were 22 boys and 29 girls; 20 were first seen under the age of 5, 15 between 5 and 10, and 16 between 10 and 16. Twenty seven children lived in the manor house, 17 miles from the district general hospital, and 24 lived at home with parents or foster parents.

Twenty seven children had the combination of severe mental handicap, severe cerebral palsy, and severe visual difficulties in addition to epilepsy. Forty five children fell into the

educational classification of severe learning difficulty and 30 were wheelchair bound. Other handicaps included autism, severe deafness, and hydrocephalus. Thirteen children had had infantile spasms, three of the children had tuberous sclerosis, and one had Batten's disease. Seven died during the period of the study.

Several children moved in and out of the area, died, or grew too old for the study. In these cases they are described under the heading 'outcome' as they were on their last visit.

Forty four children arrived with epilepsy already under treatment, which made assessment more difficult. Of these 19 were on more than one drug; two children were on three drugs concurrently. One child with photosensitive epilepsy was provided with dark glasses in sunlight, which were effective. One child with Rett's syndrome was off treatment because her mother thought she was safer on goats' milk (local folklore). The child had no choice. Treatment was begun in seven children.

Types of fit

Each child's fits were witnessed and identified as fits by at least two experienced observers before treatment was begun.

Classification of the type of fit was difficult. The 51 children had many different types of epilepsy. Fits were counted mainly by parents and care staff, occasionally by nurses, teachers, and doctors. Care staff classified fits as either grand mal or petit mal, and had to be questioned closely about the details of the minor attacks. Fits were classified as recommended by Patten (J Patten, personal communication). This classification was based on his experience with handicapped adults, and used four main groupings, which correlate well with the usual responses of the epilepsies to treatment. These were: classical petit mal (one child), complex partial seizures (26 children), fits involving myoclonus, including akinetic falls (10 children), and generalised seizures involving loss of consciousness (43 children). Several children had more than one kind of fit. This simple scheme worked well in practice, so that there was no difficulty in identifying individual types of fit on clinical grounds. Aicardi used a similar classification (J Aicardi, paper given at the Fourth International Symposium on valproate and epilepsy, Jersey, 1989). His grouping was

Table 1 Classification of patients by cause of condition (n=51)

Cause	No of patients
Genetic	13
Perinatal including hypoxia and intrauterine infection	13
Postnatal and infection	6
Cerebral malformation	5
Other	5
Unknown	9

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grand mal epilepsy, partial epilepsy due to brain damage, myoclonic epilepsy (subdivided into severe and benign), febrile convulsions (not discussed here), and West's syndrome (not applicable in this age group).

General management

The children seemed to respond to a regular life style. They were noted to have more fits on holiday or after a change of home or care staff. In contradiction to the views of O'Donohoe,⁹ three children appeared to have more fits when severely constipated. This is a difficult problem with such immobile children, but a high fibre diet, monitoring of fluid intake, and regular lactulose was helpful. One child appeared to respond to a ketogenic diet but the fits did not recur for some time after when this was subsequently stopped. These children have few things to look forward to each day, so it seems a pity to interfere with their meals on the scale necessitated by a ketogenic diet.

Parents and care staff were instructed to give rectal diazepam if any fit lasted more than five minutes. Stesolid (CP Pharmaceuticals) proved most suitable. Parents needed reassurance that their child was extremely unlikely to die in a fit.

Drug treatment

The very ambitious initial target was to reduce fits to two a year while keeping the children awake, content, and able to learn, if possible using no more than one drug in each case. This target had to be reduced to exclude short absence seizures of any kind, and attempts were made to minimise these.

It was necessary to discuss changes in medication in detail with parents and care staff. Care staff are more used to seeing patients with fits. Parents are often afraid of 'drugs', and may not give medication in which they do not believe.

The known side effects of the drugs were incorporated in the outpatient letter of which parents automatically received a copy. The risk of fits had to be balanced against side effects, especially drowsiness.

When first seen 11 children were having more than one fit a week but eight had to be woken up to eat. A frequent reason that the children were on so many drugs and so oversedated was that drugs had often in the past been increased to cover an exacerbation of fits and never decreased again. The facts that fits come in clusters, which may be followed by long quiescent periods, had not been recognised.

When children arrived on treatment their current regime was continued while fit activity and drug concentrations were monitored. Investigations were only done when clinically essential. Drug charts were reviewed each month and patients seen according to clinical need.

If fits were not controlled, the most favoured drug was increased to its maximum. If this were proved ineffective, another drug was introduced or increased, and the first drug reduced. When the child was stable, the least favoured drug was reduced very slowly, an adjustment being made every two months or so. When this had finally

been withdrawn, any other ineffective drugs were gradually withdrawn in turn until the child was on one drug. When the child had been fit free for two years, the last drug was withdrawn extremely slowly over at least four months. As far as possible treatment was kept well below the maximum recommended level, and sometimes very small doses made a great difference to the number of fits. The treatment given is shown in table 2.

At first the drugs with least side effects were used (the type of epilepsy being ignored) so that carbamazepine was the first line drug because of the anxiety about sodium valproate jaundice. This proved an ineffective way of controlling many fits, however, so that eventually carbamazepine was still used for generalised seizures as first choice, but sodium valproate was preferred for all seizures involving myoclonus and for complex partial seizures.

The effects of reduction of drugs were often first noted by the teachers, who inquired why the child was 'brighter'. The sister in charge in the children's home approved of the simplification of the drug round, and the care staff commented on the improvement in the children's alertness and noted that they were making more sounds. However two children were admitted to hospital in status epilepticus.

Drug doses were those suggested by Addy.¹⁰ The sister in the children's home preferred tablets which she crushed, but parents generally preferred sugar free liquids. In general drugs were given twice daily. Sometimes a midday dose of sodium valproate was given, and sometimes a late night dose of any drug reduced nocturnal and early morning fits, but this usually meant waking the children and was particularly unpopular where children lived at home.

Blood concentrations were used to monitor phenytoin, phenobarbitone, and carbamazepine.

Outcome

At the end of the treatment period nine (18%) had come off drugs and were fit free. Two children had been off drugs for about a year but fits recurred, 19 had no fits on treatment in the past six months, 12 were having fits less often than once a month, and three about once a week, but three children on drugs continued to have several fits a week. Of these, one had several akinetic falls each week so that he had to wear a protective helmet. Increasing any treatment made him silent and miserable. One child had tuberous sclerosis and one, with a cerebral malformation, became drowsy on all agents tried. Not surprisingly, the child on goats' milk

Table 2. Treatment according to seizure type*

Seizures type	Off all drugs	Taking one drug only	Taking more than one drug
Petit mal	1	—	—
Complex partial	2	13	11
Involves myoclonus	—	3	7
Generalised	8	20	15

*Twenty three children had more than one type of fit.

(at parent's insistence) continued to have complex partial seizures. Table 3 shows the outcome of the children, and table 4 the number of drugs given, before and after rationalisation of drug treatment.

The fits of 17 children were controlled on sodium valproate alone, four on carbamazepine alone, two on phenytoin, and one on clobazam.

Thirteen children still needed two drugs. Four were on carbamazepine and sodium valproate, two (with myoclonus) on carbamazepine and methsuximide, three (with generalised fits and myoclonus) on sodium valproate and primidone, two (with generalised fits and myoclonus) on sodium valproate and clonazepam, one on carbamazepine and phenobarbitone, and one on sodium valproate and phenytoin. One child still needed three drugs.

Cost

The daily cost of the medication was approximately the same at the end of the treatment modifications. Fewer more expensive drugs had been substituted for less expensive but ineffective agents. Initially 71 individual drug doses were given out each day but by the end of the treatment period only 57 were needed.

Side effects

The side effects of the modified regimes were surprisingly few. Thirteen children had been very drowsy on arrival, especially those on multiple treatment. One child developed erythema nodosum on phenobarbitone, two were very miserable on carbamazepine, one stopped eating on primidone. One was overactive and two miserable on diazepam (this had been used previously to reduce muscle tone). A child with tuberous sclerosis became aggressive and sleepless on everything except sodium valproate and carbamazepine. One child developed abnormal liver function tests but these returned to normal when the sodium valproate was withdrawn. No rashes and no alopecia were seen and no blood dyscrasias detected.

In this group there was no clinical problem with sodium valproate, although weight gain may be a problem with this drug. Of the 18 children still on sodium valproate at the end of the

series, there were two ambulant children whose height and weight were above the 90th centile (probably familial). One child was on the 75th for both height and weight, and three on the 50th for height and weight; two were below the 25th, three below the 10th, and seven below the 3rd for weight. These figures emphasise that poor weight gain is a serious problem in non-ambulant spastic children, so much so that some have needed gastrostomies to increase their energy intake.¹¹

Phenytoin proved to be a difficult drug to use in the multiply handicapped child because many have neurological disabilities similar to the recognised side effects of the drug, and the repeated blood tests were frightening for them, especially if they were blind. One child on phenytoin stopped eating and lost weight. The care staff noted that her tongue was rolling up in her mouth when she tried to chew. A very small (25 mg) increase in dosage had pushed her phenytoin into the toxic range and reducing the dose allowed her to eat again. Choreiform movements are a known side effect of phenytoin.⁹ Two children on phenytoin had gingival hyperplasia.

Phenobarbitone and clonazepam both caused sedation and produced behaviour problems.^{9 12} These, mainly immobile, children showed irritability rather than hyperactivity. Clobazam at night did not sedate during the day.

As so many children had more than one type of fit, it was not easy to say which fit type responded to which drug. Sodium valproate and carbamazepine were both effective in some children with generalised and/or complex partial seizures. Myoclonic seizures responded least but sodium valproate proved to be most effective for this seizure type.

The drugs in principal use were sodium valproate and carbamazepine, but phenytoin, methsuximide, phenobarbitone, clonazepam, and clobazam were used occasionally. Grand mal and complex partial seizures both responded in part to either sodium valproate or carbamazepine (this differs from the conclusions of Aicardi who regards sodium valproate as a second line drug here¹) but for a few children the older, more sedative anticonvulsants phenytoin and primidone were needed. Carbamazepine was not effective in myoclonus.

One child with gelastic epilepsy responded to carbamazepine. Exaggerated startle responses were intractable but it was possible to prevent their progression to grand mal as had occurred in two children. Previous infantile spasms proved not necessarily a bad prognostic sign; six out of 13 children who had had them had one fit a year during the observation period.

Control of epilepsy in the children in care proved as difficult as in those living at home.

Children on one drug only at the end of the series are shown in table 5.

Table 3 Outcome of children before and after rationalisation of drug treatment

	On drug treatment			No drugs: no fits	Goats' milk: frequent fits
	Frequent fits	Few fits	No fits		
Before	22	20	7	1	1
After	9	31	0	10	1

Few fits means less than one fit a month but still on drugs.

Table 4 Number of drugs given before and after rationalisation of drug treatment

	No drugs	One drug only	Two drugs	Three drugs
Before	2	27	19	3
After	11	24	15	1

Addendum

Since these figures were compiled, one year ago, one child in the 'few fits' group has died, and two children have moved from 'frequent fits' to few fits. The child who came off the ketogenic

Table 5 Patients on one drug only in each seizure group at end of series

Fit type	Carbamazepine	Clobazam	Phenytoin	Sodium valproate
Complex partial	3	—	1	8
Involves myoclonus	—	—	—	3
Generalised seizures	3	1	2	13

diet has begun to have very frequent fits and is taking acetazolamide. The child who came off primidone because of anorexia and continued to have one or two fits a week is settling down on sodium valproate and phenytoin. One child stabilised previously on sodium valproate, with complex partial seizures consisting of staring and mouth twitching, has started to have generalised fits and aphasic episodes and is responding to phenytoin in addition. One child with hydrocephalus, in the few fits group, on carbamazepine and methsuximide deteriorated and was found to have a posterior fossa tumour. A child with Rett's syndrome had an increasing number of generalised and complex partial seizures on carbamazepine but so far is responding to sodium valproate. These children therefore are continually changing and need regular review. Of the three children with fits almost daily, one had left the children's home. One with severe akinetic falls was changed from carbamazepine and methsuximide to sodium valproate (which had been tried previously unsuccessfully) and is much happier, and only having two to three falls a week. The child with tuberous sclerosis is still having almost daily fits, during which she may vomit.

Conclusions

It is possible to treat many severely handicapped children with epilepsy so that they have few fits and are not sedated. A total of 54% of the children in this series were off drugs, or controlled on one drug only without sedation. Four children remained uncontrolled (three on treatment, one on goats' milk at mother's request).

In this group it proved possible to reduce both the number of drugs used and the number of fits. The balance between control and sedation was always difficult, and it seemed more important to keep the children awake, content, and able to learn, rather than entirely fit free. Care staff were experienced with fits and relaxed about permitting brief ones. It was

possible to persuade most parents to accept that occasional short fits were preferable to sedation, provided that they had rectal diazepam to hand.

It is important to review children regularly to see if drug reduction is possible, and because the situations change. Increases to cover a series of fits need not become a permanent feature of the regime.

Sodium valproate seems to be the drug of first choice for fits involving myoclonus and for complex partial seizures in severely handicapped children over 3 years old, who have normal liver function tests, and have no suggestion of a biochemical cause for their condition. Carbamazepine is the first choice in generalised seizures with sodium valproate being substituted if carbamazepine fails. Rationalising drug treatment did not increase expenditure.

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REGULAR REVIEW

The human genome: a prospect for paediatrics

R M Gardiner

The revolution in molecular biology has generated methods that will almost certainly allow the organisation of the human genome to be understood in detail before the new millennium is more than a decade or two old. A task that seemed unapproachable a few years ago is now seen by optimists as one that might be completed within the foreseeable future. Each month it seems that another disease gene has been mapped, if not cloned, and plans to determine the sequence of all three billion base pairs of the human genome have been made. How has this come about, how will further progress be made, and what are the implications for the health of children?

The scientific methods that have given rise to the 'new genetics', and the implications of this revolution for clinical practice, have been admirably reviewed elsewhere.¹ It is clear that the scale on which disease is understood has shifted down to the molecular level, and that this has in a sense undermined the old physiological and anatomical boundaries defined by organ systems. This new approach is not surprisingly thrown into sharpest focus in the field of human genetic disease, but its ramifications spread far beyond an increased understanding of some collectively numerous, but individually rare, inherited disorders. Of central importance, nevertheless, is the new capacity to map, and subsequently to isolate, disease genes known only by their phenotype.

This capacity arises from a fusion of classical genetics and molecular biology. In essence, the identification of an unsuspected and vast resource of genetic polymorphism at the DNA level has rendered the human species accessible to linkage analysis, an old genetic tool previously reserved for easily interbred species such as flies and mice.

The mere localisation of genes—gene mapping—is of limited interest. Apart from some clustering of genes into families, there is nothing so far to suggest that the geographical distribution of loci is other than random. In parallel with this new capacity to localise genes, however, a set of methods has arisen that allow genes—once they are localised—to be isolated and characterised. The protein encoded and its defect can then be determined—so called 'reverse genetics'.

The extraordinary revolution that has occurred is best understood by considering briefly our current state of knowledge of the human genome and gene map, the history of linkage analysis, the meaning of genetic polymorphism, and the development of techniques that allow its detection at the level of DNA, achievements in

applying these methods to human inherited disease so far, and the prospects for the future.

The human genome

The human haploid genome comprises about three thousand million base pairs; this is comparatively large. The complete sequence of the simple bacterium *Escherichia coli*, a mere five million base pairs, has yet to be determined.

As a typical protein comprises say, three hundred amino acids, only one thousand nucleotides are required on average for a structural gene's coding region. The human genome, therefore, has sufficient DNA to encode several million genes. It is probable, however, that no more than 5% of a mammalian genome codes for protein. The rest is accounted for by highly repetitive sequences with no obvious function, and the introns (non-coding regions between the exons or coding regions), and flanking regions, which make up the main part of individual subject's genes.

It has been estimated that the human genome codes for between 50 and 150 000 protein products clustered into 5 to 10 000 related families. McKusick's catalogue of mendelian traits has about 4000 entries: gene loci identified by their phenotypes. The chromosomal locations of several hundred of these are known, and the region in which many reside has been identified. About 500 genes have been cloned, but the detailed fine structure of their genomic organisation is known for only a mere handful.

Most of man's genes have not yet been identified—let alone mapped, cloned, and sequenced. The procedure for identifying the gene for a particular protein is relatively straightforward. Antibodies can be used to screen a library of genomic fragments corresponding to regions that are expressed—that is, code for proteins. The corresponding gene can then be identified. Localisation to a particular chromosome and region is then a relatively simple matter. Most disease genes, however, are known only by their phenotype; their biochemical basis is unknown. It is to these disorders that linkage analysis can now be applied. The intention is not merely to map disease loci but, having done so, to isolate the defective gene itself and determine its function and molecular pathology.

Linkage analysis

Linkage may be defined as the occurrence of two loci sufficiently close to each other on a chromosome that their assortment (that is, distribution to germ cells) is not independent.

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A human cell contains 23 pairs of homologous chromosomes, one of each pair inherited from the father and one from the mother. During meiosis, homologous chromosomes are duplicated and then distributed among four germ cells. Alleles at loci on different chromosomes are inherited together by chance in half of all meioses. Alleles at loci on the same chromosome would always be inherited together if it were not for the phenomenon of recombination, or crossing over.

During meiosis homologous chromosomes repeatedly exchange segments of equal length. This process of recombination, or crossing over, occurs at least once for each chromosome, with perhaps 50 meiotic exchanges in each chromosome set in each generation. Sturtevant, in T H Morgan's laboratory, was the first to recognise that the closer together two loci lie on the same parental chromosome, the less often their alleles are separated by recombination during meiosis (in Morgan's honour his name was given to the unit of genetic distance: loci that recombine in 1% meioses are said to be one centimorgan (cM) apart). Inheritance patterns of alleles at two loci—linkage analysis—could be used to determine the relative positions of genes along a chromosome, and the first genetic map, of five sex linked loci in *Drosophila*, was produced.

This approach was highly successful in studying mutations in genetic systems that allowed extensive interbreeding of mutant stocks, and complete linkage maps were constructed for several species. Unfortunately its application in man was severely limited for several reasons.

In the human species, information is limited to that arising from random mating through a limited number of generations. This is a severe restraint, but more importantly, mapping of a disease trait requires comparison of its inheritance with that of a genetic marker of known location. Such markers must both be readily detectable, and found in a number of distinguishable variants (polymorphisms) throughout the population. Until recently such markers were limited to a few proteins that displayed limited polymorphism and were representative of only a tiny fraction of the genome. Of course, X linkage was easily identifiable and a few diseases were mapped by linkage analysis, but for all practical purposes construction of a genetic map was impractical. It was the advent of recombinant DNA technology that transformed linkage analysis into a powerful tool for genetic analysis in man. Genetic polymorphism became detectable at the level of DNA rather than of proteins.

Genetic polymorphism and DNA markers

In the terminology of classical genetics a polymorphism is 'the existence in the same habitat at the same time of two or more distinct forms of the species' (E B Ford). In more modern terms it is 'the occurrence of two or more alleles for a particular locus where at least two alleles appear with frequencies of more than one per cent'. At the most basic level, polymorphism

reflects a difference in the base sequence at the pair of alleles on homologous chromosomes at a particular locus.

It is now recognised that there are several million single base change differences between the two haploid genome sets found in each cell of an individual subject, a difference in sequence occurring every 200–600 base pairs. This extensive variation represents an unsuspected vast resource of genetic polymorphism that can easily be detected. Most of these differences occur in 'neutral' DNA, between genes rather than in coding sequences. The sequence changes are said to be 'neutral' because they are passed from generation to generation without any effect on phenotype or on survival.

'Restriction enzymes' provide a practical means of detecting these variations in DNA sequence between homologous chromosomes. A particular restriction enzyme cuts the genome into millions of fragments, not in a random fashion but cutting whenever the base sequence (usually four or six) that defines its restriction site occurs. Variation in the DNA that creates or eliminates a restriction site, or alters the length of DNA between the two particular sites, alters the length of the resulting DNA fragment. This restriction fragment length polymorphism (RFLP) can be detected by Southern blotting.

The problem is the detection of those specific fragments corresponding to the probe in question among the millions generated by digesting genomic DNA. The fragments can be separated according to size by electrophoresis in a gel and 'blotted' on to a sheet of nylon membrane. The filter is exposed to the probe DNA previously labelled with a radioisotope, and this 'hybridises' to fragments bearing the complementary sequence of bases. It is the extraordinary specificity of the hydrogen bonding between complementary base sequences that underlies the power of this method: there are few biochemical reactions with comparable sensitivity and specificity. The location of the hybridised radioactive probe is identified by autoradiography allowing the fragment sizes for an individual subject to be shown.

So that recombination may be detected between a disease locus and a marker locus, the subject in whom the meiosis under study has occurred must be heterozygous at the marker locus. The value of a marker in linkage analysis is therefore critically dependent on how many variants it displays in the population, and therefore the likelihood of a given subject being heterozygous. RFLPs resulting from the presence or absence of a restriction enzyme site exist in only two forms so at least half the population will be homozygous and the meioses studied are often uninformative. More recently, a second variety of polymorphism has been identified, which gives rise to multiple allelic variants. In this case the RFLPs arise from variation in the number of 'tandem repeats' of a DNA sequence between restriction sites. For these so called 'variable number tandem repeat' probes the odds that an individual subject will carry different alleles on the homologous chromosomes are much higher.

Linkage map of the genome using DNA markers

The first DNA polymorphism that gave rise to a variation in length of restriction fragments was recognised 10 years ago. The potential importance of this observation was soon recognised: the existence of millions of single base change differences between homologous chromosomes could provide a limitless supply of markers scattered throughout the human genome. The approach was set out in detail in 1980.² Several laboratories set out with the deliberate aim of producing a complete linkage map of the human genome using DNA markers. How has this been done? At the outset it was uncertain how many such polymorphic DNA markers it would be possible to identify, and how many would be necessary to cover the genome.

Linkage between markers can be established by following their inheritance in so called 'perfect' families. Maximum information is gained from studying families with four grandparents, two parents, and an average of eight children. An international collaboration was set up in 1984 called the Centre d'Etude de Polymorphisme Humain (CEPH), which maintains cell lines (a renewable source of DNA) on many such families. The Mormon families of Utah have been a particularly fruitful source of such pedigrees.

A huge and expensive effort has been necessary to generate and map the several hundred markers now available. Clones from a 'library' of human genomic DNA are tested to see whether they detect an RFLP. Their inheritance pattern is then studied in the 'perfect' families to identify linkage groups. Linkage groups can be assigned to a specific chromosome if they contain a probe the chromosomal location of which had been previously determined. The actual mapping—determining the arrangement of markers along a chromosome and the distances between them—entails a massive mathematical exercise for which new computer algorithms were designed.

The 'ideal' linkage map would be comprised of highly informative markers spaced evenly at intervals of 10 cM and covering the entire genome. Markers presently available fall somewhat short of this ideal, but few doubt that it will soon be attained. Publication by one research group of details of a collection of markers referred to as 'a genetic linkage map of the human genome' created a furore in 1987. Although it was estimated that this 'map' was detectably linked to 95% of the DNA in the human genome, the fact remains that several chromosomes contain regions in which the linkage groups are not connected. The intense and public acrimony generated by the publication of this 'map' reflected in part the strong commercial pressures generated in this field. Considerable further work is required to generate a map in which most of the markers are highly informative, and sufficiently close together (1 cM), to provide close enough linkage to act as a starting point for cloning genes.

Disease genes linked to DNA markers

Gene mapping in man by linkage analysis has,

of course, a long history. Assignment of the genes for colour blindness to the X chromosome was noted as early as 1911,³ and a number of diseases genes were subsequently assigned to this chromosome because of their sex linked pattern of inheritance. Progress in the application of DNA methods to localisation of disease genes on the X chromosome has been rapid, aided of course by the head start of knowing which chromosome to investigate.

The first autosomal linkage in man was reported in 1951,⁴ but subsequent progress was slow. The search for DNA markers linked to disease loci that were known to be autosomal has been marked by almost unbelievable luck. For various reasons linkage analysis is easier in dominantly inherited conditions. Linked markers were found among the first few examined in Huntington's chorea⁵ and adult polycystic kidney disease.⁶ Autosomal recessive disorders are a more daunting prospect, as the possibility of non-allelic heterogeneity cannot be discounted in advance. Linked markers have nevertheless been found in at least four such conditions—Friedreich's ataxia,⁷ ataxia telangiectasia,⁸ Batten's disease,⁹ and cystic fibrosis.¹⁰ The last named is, of course, perhaps the most common and important genetic disorder in white populations. Although, as it happens, the first linkage to cystic fibrosis was found to a protein marker (para-oxonase), localisation was achieved simultaneously by showing linkage to DNA markers on chromosome 7.

Subsequent work has led to mapping of a number of disease genes using this approach including neurofibromatosis, tuberous sclerosis, familial Alzheimer's disease, atopy, and several psychiatric disorders. The problem of non-allelic heterogeneity—identical phenotypes arising from mutations at separate loci—has emerged in some disorders.

Identification of a linked marker does not, of course, hand you the gene. The immediate practical benefit accrues from its use in prenatal, preclinical, and carrier diagnosis. Depending on the recombination frequency between marker and disease gene, the physical distance between the two may be anything between 1 and 10 million base pairs. The task of moving from linked marker to identification of the disease gene itself represents a distinct technical challenge as the method of linkage analysis is no longer applicable at genetic distances so close that recombination is an infrequent event.

Isolation of disease genes

Genetic linkage analysis allows localisation of a disease gene to within 1 to 10 cM, a genetic distance corresponding to a huge physical distance of several million base pairs. Nevertheless, isolation of several disease genes by this approach of 'reverse genetics' has now been achieved. These include Duchenne muscular dystrophy, chronic granulomatous disease, retinoblastoma, von Willebrand's disease, and—most recently and famously—cystic fibrosis.¹¹⁻¹³

The initial successes were achieved by the ingenious exploitation of cytogenetic alterations identifiable in affected subjects. Clues to the

precise location of the disease gene were provided by large and identifiable rearrangements of the surrounding DNA. Deletions were particularly valuable.

Pessimists dismissed the isolation of disease genes in which the mutation was a subtle alteration (such as a point mutation) as potentially impossible. They had good reason. An apparently unbridgable 'resolution gap' existed between the scale of linkage mapping information and that encompassed by available cloning methods. Linkage data could identify a region of several million base pairs encompassing the locus of interest, but this could only be sifted through in tiny steps of a few thousand base pairs each—a daunting task for even the most masochistic molecular biologist. Moreover, it was difficult to know in which direction a 'chromosome walk' might be proceeding, and not obvious how one would recognise a particular DNA sequence as a disease gene.

In the last five years several techniques have been developed that bridge this gap. 'Rare cutter' restriction enzymes became available, which cut mammalian DNA infrequently and therefore generate much larger individual fragments. The technique of 'pulsed field' gel electrophoresis was developed, which allowed the size of fragments resolved by electrophoresis to be increased from about 25 kilobases to several million base pairs. A method for cloning the 'ends' of long DNA fragments selectively was devised, which allows probes to be constructed that permit the identification of a genomic fragment at some considerable distance from an initial marker—so called 'chromosome jumping'. Lastly, new vectors (yeast artificial chromosomes—YACs) have been developed that permit cloning of DNA fragments up to a million base pairs in length, substantially larger than was previously possible.

If markers have been identified that 'flank' a disease locus it is therefore now possible to search the intervening region systematically by sequential cloning and analysis until the disease gene is identified. Ultimate success is assured. The researchers know that the gene is there, in the freezer; it is simply a matter of identifying which of the racks of plastic test tubes in there contain it. The power of this approach has been illustrated by the recent isolation of the cystic fibrosis gene. Markers flanking this gene were identified in 1985. Subsequent work narrowed the region of interest to about 1 000 000 base pairs. The winning teams 'jumped' and walked along 280 kilobases of DNA before the edge of the cystic fibrosis gene was reached, and a further 250 kilobases of DNA had to be isolated and characterised to identify the gene. They were able to show that the mutation causing the disease in 70% of patients is a 3 base pair deletion that removes a single phenylalanine residue from the encoded protein. This achievement should not be underestimated by comparisons with finding a needle in a haystack. It is analogous to finding a needle dropped anywhere on a 3000 mile highway—the distance from New York to San Francisco.

Isolation of the disease gene then allows the precise molecular genetic pathophysiology of

the disease to be determined. Not only can the defective protein product be identified, but the nature of the defect can be analysed in the detail currently available only for the thalassaemias and a few other disorders. This has several important consequences. First, identification of the mutation at the DNA level opens up the possibility of population screening. This will apply only to common disorders, but for diseases such as cystic fibrosis with a gene frequency of one in 20 in white populations the case for screening explains some of the commercial interest in isolation of the gene. Secondly, identification of the protein product and clarification of the biochemistry entailed may allow design of new and rational strategies for treatment.

Future prospects

The task of mapping, isolating, and characterising all man's genes is immense but finite. It is likely that a high resolution map of linked markers covering the entire human genome will be available within a few years. The suggestion has arisen that, parallel to this effort, the complete base sequence of the human genome—all 3000 million base pairs—should be determined.¹⁴ The background and implications of this proposal are worth considering.

The nucleotide sequence of a genome represents a physical map at the highest degree of resolution. The scientific justification for wishing to know the entire sequence is uncertain, as it is known that coding genes and their regulatory sequences comprise only about 5% of the genome. It has been argued therefore that initial effort should go into determining the sequence of the expressed portion, as represented by cDNA clones. It seems likely, however, that the unexpressed regions will contain unsuspected sequences with important functions. Of equal concern is the difficulty in handling the sheer volume of information generated by a complete sequence. So far, about 15 million nucleotides of DNA sequences have been accumulated, of which about 2 million are from human DNA. This latter figure represents only 0.07% of the total. Storage and analysis of millions of nucleotides of sequence will be a huge task, even if advances in methods occur that allow the rate of analysis to be appreciably increased: with current technology the task would take about 30 000 technician years. Cynics have suggested that it would be cheaper to store the sequence in DNA than to extract it from the DNA for storage in computers.

Whether or not the entire sequence is ever determined, it seems likely that physical maps and complete sequences of specific regions or even whole chromosomes will become available within the foreseeable future. What are the implications for paediatrics?

It seems safe to predict that there will be an exponential increase in our understanding of the genetic contribution to disease. The molecular genetic basis of most single gene disorders is now amenable to investigation, and will surely be revealed. In addition to these disease genes, a host (if not all) of the genes that specify a human

being will be identified with corresponding increases in our understanding of the biology of man. Increased understanding does not of course always lead to practical benefits. A molecular understanding does not guarantee a molecular approach to prevention or cure: sickle cell disease stands witness to that sad fact. Nevertheless it is reasonable to be optimistic that more effective approaches to avoiding these diseases will be developed even if treatment based on our new understanding is more difficult to devise.

Perhaps the most exciting prospect is the possibility of increased understanding of those common disorders that have a genetic component in their aetiology but are not determined by a single gene and may require an appreciable environmental contribution. Complex phenotypes that arise from interactions between several genes, and between genes and the environment, include a number of important childhood conditions such as asthma, epilepsy, diabetes mellitus, and certain congenital malformations. These multifactorial diseases are more difficult to analyse than those attributable to single genes, but the task is no longer impossible. As the number and power of the DNA markers that are available remorselessly increases, these diseases are becoming amenable to investigation. Not only is the number of families required to generate sufficient informative meioses reduced, but entirely new strategies, such as multilocus analysis and simultaneous search, emerge that can overcome—at least in theory—the hitherto insoluble complexities arising in attempts at linkage analysis of multifactorial diseases.

It is indeed ironic that the most profound revolution in biological methods since the invention of the light microscope should coincide with a period of retrenchment in medical research funding. It is no coincidence that a pattern has emerged in which genes are mapped in the United Kingdom, but isolated in the

United States. The latter process is as expensive and labour intensive as formula I motor racing. Winning is difficult if the sponsor will only provide a bicycle.

The 'human genome' today is as much a 'dark continent' as Africa in the early 19th century. Its exploration is about to begin. Genetics has become much too interesting and exciting to leave to the geneticists. Of all the research challenges confronting research minded paediatricians this must surely be the least trivial pursuit.

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CURRENT TOPIC

Choice of sleeping position for infants: possible association with cot death

A C Engelberts, G A de Jonge

The sleeping position of infants may seem a trivial aspect of baby care. Because of a possible association with cot death, however, it deserves serious consideration. Different positions have been strongly advocated and it seems that opinions differ widely among countries and change over time. In contrast to the strong opinions is the paucity of research and published reports on the actual benefits and possible dangers of the various sleeping positions. We therefore reviewed the available data about the sleeping position to try and give an answer to perhaps one of the most elementary questions of baby care: how do I place my baby in its cot?

Sleeping positions

There are four more or less stable positions in which an infant can sleep: supine, on its side, prone with the face turned to one side, or prone face down. Obviously infants are rarely placed face down with their noses on their mattresses, although some parents may eventually do so after repeatedly finding their infant in such a position. The sleeping position is determined by several factors: the position in which an infant is placed, the motor abilities that are developing with the age of the child, and the clothing and bedclothes that may restrict movement; the child's movements are also influenced by various factors such as dyspnoea and illness.

The development of an infant's ability to turn has been widely studied, although almost exclusively when awake, and not when the infant is presumably asleep. Hassall and Vandenberg, however, surveyed the positions in which more than 4000 babies in New Zealand from 1 to 4.5 months of age were usually placed, and those in which they were later found.¹ The side position was the least stable, with 47% of the 1 month old babies placed on their sides being found in a different position. As the age of the infants increased, parents more often placed them in the more stable prone or supine position, probably because babies do not stay on their sides for long. Even in the prone and supine positions 14% and 10% of infants up to 4.5 months of age, respectively, changed position, and as many as 3% of the 1 month old infants who were placed prone managed to end up on their backs.

In a survey that we conducted in the summer of 1988, parents of 406 infants aged from 2 weeks to 8 months were asked at 'well baby' clinics how they had put their infants to bed the

night before, and in which position the infants were found that morning. Of the 227 infants not yet 4 months old, 123 (54%) had been placed laterally. Only 37 of these laterally placed infants (30%), however, were still on their sides the next morning: 80 (65%) had turned to supine, five (4%), had turned to prone, and in one (1%) the position was unknown. In the same age group 38 infants were placed prone (17%); none turned to another position. Of the 66 infants placed supine (29%) only two turned (3%); all were 3 months old and all ended up prone. In the age group 4 months and over there were 179 infants. The lateral position was even less stable than in the younger age group: of the 16 infants placed on their sides, 13 were found supine, and in three the position was unknown. In this older group 137 infants (77%) were placed supine of whom 118 (86%) remained supine; 26 infants (15%) were placed prone of whom 21 (81%) were found still prone the next morning.

Benefits and disadvantages of various sleeping positions

In 1960 the English paediatrician Holt wrote that it was common practice in the United States to place babies prone, while he could not recall an English mother doing so.² The most common reasons given by the American mothers were that the infant was more comfortable and that it was safer in case of vomiting—arguments that are often heard today. Holt described the arguments as 'interesting' but doubted that they would 'stand critical scrutiny', probably influenced by his experience that the English babies placed supine fared quite well. Although doctors have changed their opinions about the best sleeping position for babies from time to time and place to place, it is curious that the actual benefits and disadvantages have received so little 'critical scrutiny'. The following considerations have been put forward:

(1) The most thoroughly researched reason for placing an infant prone is to prevent gastro-oesophageal reflux. The prone, and in particular the prone position with the head raised, has conclusively been shown to significantly reduce the amount of reflux in symptomatic and asymptomatic infants.³⁻⁷ Gastro-oesophageal reflux in asymptomatic infants, however, seems to occur mainly in the first two postprandial hours and rarely during sleep.^{8,9} In Western countries it is often thought that infants who sleep supine are also at greater risk of vomiting

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and aspiration, although this has not been established.¹⁰

(2) Research has also been carried out into the association between the position of an infant and his or her pulmonary function, and various advantages of a prone position have been postulated.¹¹⁻¹⁸ Two reports have mentioned the energy expenditure in various positions, with contradictory results.^{16, 17} There has been no study to our knowledge concerning the possible long term effects of a prone or a supine position. The influence of body position on the pulmonary function of infants is still unclear and further studies are required; furthermore, it does not seem wise to extrapolate findings from studies of preterm infants to infants born at full term. For preterm infants, however, sleeping prone may be advantageous during the neonatal period; a recent editorial in the *Lancet* suggests weighing individual considerations and adopting an empirical approach.¹⁸

(3) Placing an infant prone can have certain orthopaedic advantages. The prone position might prevent infantile scoliosis, although this is not certain.¹⁹⁻²¹ Lying prone can probably prevent limitation of hip abduction; this seems to be induced by a habitual semilateral supine position on the same side and needs no treatment except to encourage another position. Subsequently the hip joint will develop normally. Sleeping prone has no preventive effect on the more serious congenital dislocation of the hip.²² Placing an infant prone, especially in the knee-chest position, may cause tiptoe walking and a turning in or turning out of the feet. These faulty alignments of the feet and legs usually correct themselves when the child starts to walk.^{23, 24} Furthermore, a habitual lateral or supine position may cause moulding of the skull.

(4) Placing an infant prone has been considered advantageous for the motor and even psychological development of a child.^{2, 25} Holt is, however, one of the few who actually carried out a study into this aspect of motor development. It seems that in children who habitually lie prone, the extensor phase of motor development is more advanced than the flexor phase, and these infants crawl and stand one to several months earlier than infants who lay supine, and start sitting at the same time as they start crawling. Infants who are usually supine have better head control and sit up earlier, and start sitting some time before they start crawling. Even if one agrees that the prone motor development is preferable, it is likely that these considerations apply to the position in which a child is placed when awake and active, not when asleep.

As for the psychological development of infants, to our knowledge there have been two controlled studies on the psychological effects of positioning.^{26, 27} Brackbill *et al* studied 30 infants for two hours: prone infants slept more, cried less, and moved less.²⁶ Keitel *et al* placed each newborn infant admitted to their nursery either prone or supine in rotation.²⁷ After a four day period they found that the supine infants had more nappy rashes and self inflicted scratches, and cried twice as much as the prone babies.

(5) Infants suffering from the Pierre Robin syndrome should be nursed prone because they develop 'pseudo' macroglossia as a result of the abnormal anchorage of the tongue and the reduced buccal cavity. Under the influence of gravity the tongue can obstruct the oropharynx when these infants are placed supine.²⁸

(6) A common argument in favour of placing an infant prone is to soothe 'three months colic'. Illingworth described in 1954 that placing an infant prone usually brings some relief.²⁹ Although this has often been mentioned since, we know of no controlled study. Perhaps the same mechanism is responsible as described by Keitel *et al* in their group of infants who presumably did not have colic—namely that over half of the infants stopped crying when placed on their stomachs whereas infants who cried while lying prone only occasionally stopped when placed supine.²⁷

The possibility of an association between cot death and the position in which an infant has been placed for sleep deserves serious consideration. This is not a subject that lends itself easily to prospective trials, both because of the low incidence of cot death (which would entail enrolling thousands of infants), and because of the nature of cot death itself. Several epidemiological studies have been conducted, however, and research has been carried out into the possible mechanisms that could explain such an association. There has also been some work into the correlation between trends in sleeping position and trends in the incidence of cot death. The following body of evidence links cot death to the prone sleeping position.

Association between sleeping position and cot death

The earliest epidemiological studies did not show a clear association between cot death and the infant's sleeping position. Carpenter and Shaddick reported that affected infants were found face downward more often than was to be expected from their usual sleeping habits or those of controls; the association was not significant, however, after discriminant analysis.³⁰ Froggatt's classic epidemiological study did not show a significant association between sleeping prone and cot death.³¹ The prevalence of this sleeping position was very low however, both in the series of index cases (7%) and in the series of reference cases (4%); sleeping supine, on the other hand, did occur significantly less in his group of cot deaths. Bergman *et al* reported in their study from King County, Washington, USA, that the distribution of sleeping positions (among cot deaths) was 'typical of infants in general in our community', but gave no details on how the information was obtained.³²

Recent reports have suggested that a renewed appraisal is necessary. Kahn *et al* found a significant difference in sleeping position between babies dying of the sudden infant death syndrome (SIDS) and 'near miss' children; they did not, however, find a difference between SIDS infants and their controls.³³ This study included both Belgian and French infants, and

Studies that mentioned the sleeping position of infants that died of SIDS

Author	Country and dates	Infants that died of SIDS		Reference group		Statistical testing
		Total No	Sleeping position	Total No	Sleeping position	
Carpenter and Shaddick ³⁰	England 1958–61	82	'found face down rather more'	146	Not stated	'Not significant'
Froggatt ⁴¹	Northern Ireland 1965–7	148	7% Usually prone	148	4% Usually prone	'Not significant'
Bergman <i>et al</i> ¹²	King County, Washington, USA 1965–8	170	50% Found prone	Not stated	'Similar percentage prone'	Not stated
Nicholl and O'Cathain ⁴⁶	United Kingdom 1976–9	265	42% Usually prone	273	25% Usually prone	Relative risk 2.2
Kahn <i>et al</i> ⁴³	Belgium and France 1977–82	73	71% Usually prone	177	68% Usually prone	'Not significant'
Saternus ⁴⁷	Cologne, Germany 1974–84	75	81% Found prone	306	40% Usually prone	p<0.01
Beal ⁴⁴	Adelaide, Australia 1970–84	133	8% Placed supine	152	23% Placed supine	Not stated
Tonkin ³⁸	Auckland, New Zealand 1972, 1973, and 1981	91	56% Found prone	1882	29.5% Usually prone	'Not significant'
Cameron <i>et al</i> ³⁹	Melbourne, Australia 1980–2	208	69% Prone	393	41% Usually prone	p<0.001
de Jonge <i>et al</i> ⁴⁰	The Netherlands 1980–6	142	85% Placed prone	320	62% Usually prone	p<0.0001 Relative risk 3.2
Sénécal <i>et al</i> ⁴¹	Rennes, France 1984	20	85% Placed prone	318	30.5% Usually prone	p<0.001
Lee <i>et al</i> ⁴²	Hong Kong 1986–7	16	44% Usually prone	32	6% Usually prone	p<0.01, odds ratio 11.67
McGlashan ⁴³	Tasmania 1980–6	164	58.5% Usually prone	329	42.9 Usually prone	p<0.001

this might have confounded the comparison of sleeping positions, as it is difficult to assess the influence of local traditions. Beal⁴⁴ and Davies³⁵ compared the incidence of SIDS in various countries and found lower incidences in communities that usually place their infants supine. A review of case-control studies of SIDS that mention sleeping position is given in the table. With the exception of the study of Bergman *et al* the studies showed that the prone sleeping position was more common among cot deaths, although this trend was not always statistically significant. Studies did not often specify whether the habitual sleeping position, the position in which the infants were last placed, or the position in which the infants were found was studied, which makes comparisons difficult. Furthermore, while it is necessary to take into account local traditions and the age of the infants when choosing a reference group, it is unclear if this was always considered.

Hypotheses concerning sleeping position and cot death

Though it seems clear that there is an association between sleeping prone and cot death it is difficult to prove a causal relationship. If there is a mechanism by which one can envisage such an association this would make causality more plausible. If a prone sleeping position is a causative factor in cot death, it obviously does not cause a cot death on its own and it is not a factor in all cot deaths, but it might be a preventable aspect of the complicated sequence of events leading to a cot death. Several hypotheses have been published that offer possible explanations.

Tonkin proposed that cot death could be caused by occlusion of the infant's airway at its vulnerable oropharyngeal level.⁴⁴ She stated that there were certain factors that could cause this occlusion, such as the mandible and tongue being pressed backwards by the weight of the infant's own head on the mattress. This posterior movement of the jaw is possible because of the shallowness of the temporomandibular joint in infancy, and is facilitated by the low muscle tone during sleep. When the mandible is

pressed backwards the tongue moves with it, and can obstruct the oropharyngeal airway behind the soft palate. Several studies have been published that support this hypothesis.^{45–47} Cross and Lewis found that pushing the jaw backwards or raising the floor of the mouth could cause respiratory obstruction, while not disturbing the infants sleep.⁴⁵ Orr *et al*, however, found no significant difference in the occurrence or duration of central or obstructive apnoeic events whether the baby was in the prone, supine, or lateral position.⁴⁸

Harding stated that the cartilage of an infant's nose is more compliant than that of an adults and could be more easily deformed by the weight of the infant's own head when lying prone.⁴⁹ Tonkin and Partridge suggested that even incomplete obstruction of the nose could cause complete respiratory obstruction.⁵⁰ If the diameter of the nasal passage is lessened—for example, by infection or external obstruction—the air flow must be increased. The faster the flow the greater the drop in pressure during inspiration, which could conceivably lead to collapse of the soft unsupported part of the respiratory tract, namely the oropharynx. Emery and Thorton noted an increase in the resistance to airflow in infants lying nose down.⁵¹ Although a substantial proportion of babies are able to switch to mouth breathing in case of nasal obstruction,⁴⁹ there is also a group of infants who fail to do so^{49, 52} and the ability seems to diminish in the first few months of life. At an age of 5–6 months, however, the mouth breathing reflex is established in most children.⁵² Emery and Thorton also investigated the degree of obstruction to airflow by various external factors in a baby's cot such as mattresses, pillows, and their coverings; perhaps a small part of the association between the occurrence of cot death and lying prone must be put down to these factors.⁵¹

A different hypothesis concerns the circulation in the large vessels in the neck of infants. Gilles *et al* suggested that there might be a correlation between extreme head extension and SIDS.⁵³ When dissecting the atlanto-occipital regions of infants who died of SIDS they often found a disproportion between the size of the posterior

arch of the atlas and the size of the foramen magnum. As the head was brought to the end of extension on the atlas, the posterior arch could invert through the foramen magnum to such an extent that direct pressure was brought to bear on the medulla, and the vertebral arteries were compressed. They proposed that this mechanism could lead to repeated episodes of hypoxia thus causing the morphological changes of chronic hypoxia found in SIDS. Saternus *et al* carried out flow measurements in the large neck vessels at necropsy to try to demonstrate position dependent cerebral hypoxia.⁵⁴ The combination of flexion/extension with rotation caused a large decrease in flow with repeated stoppages, particularly in the vertebral arteries. The authors recommended abandonment of the prone sleeping position, in which the head and neck of an infant often assumes these angles, and expressed a preference for a lateral positioning of infants. This hypothesis is not supported by a recent study of Lawson *et al* in which the cerebral oxidative metabolism was assessed in vivo by means of ³¹P nuclear magnetic resonance spectroscopy and no change was found after a change in head position.⁵⁵

The most recent hypothesis that takes into account the association between a prone position and cot death is that of Nelson *et al*.⁵⁶ They postulated that a combination of several cultural infant care practices could cause hyperthermia. For example, the combination of excessive wrapping and clothing, combined with a raised metabolic rate as a result of mild infection, together with a prone position that reduces heat loss and enables caudal mobility under bedding, could lead to hyperthermia.

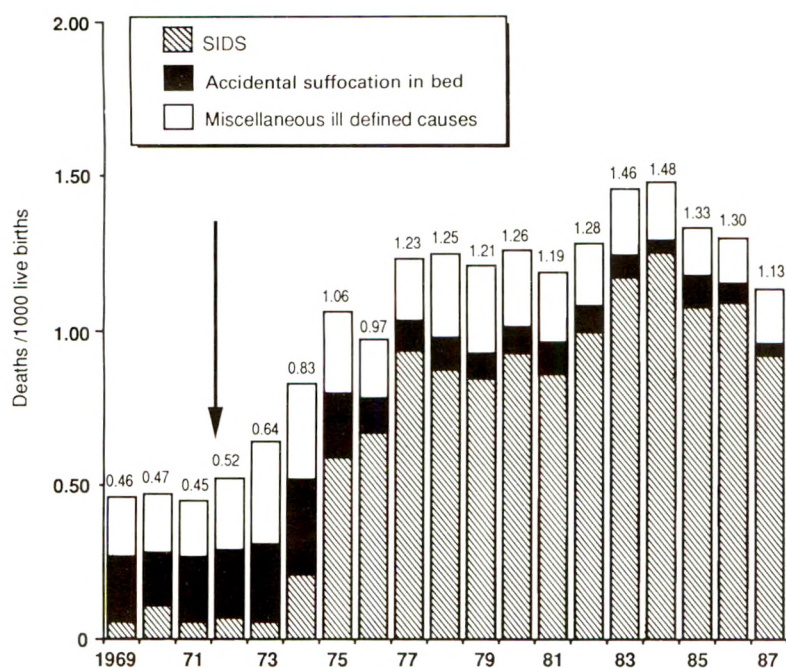
Although the mechanism by which a prone position might contribute to a cot death is not immediately clear, the above hypotheses do give biological plausibility to the association. The oropharynx is the vulnerable part of the upper respiratory tract in infants, and obstructive apnoeas often occur there.⁵⁷ We believe, therefore, that the hypotheses concerning the way in which lying prone could facilitate obstruction at this site, by either backward pressure on the mandible or partial external or nasal obstruction, merit special attention.

Trends in fashions of sleeping position and incidence of cot death

Although following two trends in time can never prove the causality of an association, a correlation between trends can give strong supportive evidence. This is the next step after comparing incidences between different countries, as Beal and Davies have done, because at least some important cultural differences are controlled for in this manner.

It used to be customary for Dutch infants to be placed on their sides or their backs when being put to bed. This changed, however, after the presentation of Reisetbauer and Czermack at the 13th International Paediatric Congress in Vienna in 1971, and their publications on this topic.²⁵ Their arguments in favour of the prone position convinced many Dutch paediatricians, and this position became fashionable, with both the Dutch medical⁵⁸ and popular press advising the prone position as the most healthy one for newborn and older infants in 1972. In this way, prone became the most common sleeping position for babies in The Netherlands. Regrettably such trends are rarely well documented: the only available reference is Swaak who stated that in 1982, 52% of 1 month old babies in the province of Noord Brabant at least occasionally slept in a prone position.⁵⁹

The registered incidence of cot death and its related causes has increased dramatically in The Netherlands over the last 15 to 20 years (figure). Whereas in 1969/71 cot death accounted for 0.46 deaths/1000 live births, the registered incidence was 1.3/1000 live births in 1986, with a postperinatal mortality of 3.8 and a total infant mortality of 7.8/1000. Both changes in coding (in January 1979 the eighth revision of the International Classification of Diseases (ICD) was replaced by the ninth), and changes in certification as a result of greater familiarity of physicians with cot death, make it difficult to draw conclusions regarding a possible increase. Baak and Huber, however, concluded at the time that the low incidence in The Netherlands in 1969–71 was probably real; even if 10% of all other probable categories of infant death were undiagnosed SIDS, the incidence would not have been more than 0.53/1000.⁶⁰ Even if one takes an extremely exaggerated estimate and considers 40% of all deaths in these categories under which SIDS could conceivably be hidden (for example, infective diseases, or diseases of the respiratory or digestive tract) to be SIDS, the incidence would then have been 0.84/1000: still much lower than the present Dutch inci-



Deaths from SIDS and associated causes during the first year of life/1000 live births in The Netherlands 1969–87. ■: Sudden death (cause unknown), cot death, SIDS; 1969–78 International Classification of Diseases (ICD) No 795.0, 1979–86 ICD No 798.0. ■: Accidental mechanical suffocation in bed or cradle; 1969–87 ICD No E913.0. □: Miscellaneous ill defined causes; 1969–78 ICD No 796.0/796.2/796.3/796.9/E913.9, 1979–87 ICD No 798.9/799.0/799.9/E913.8/E913.9. The arrow indicates the time introduction of the prone sleeping position in The Netherlands.

dence. Consequently, the Dutch rise in SIDS cannot be explained by certification errors alone. The increased neonatal survival of premature babies, a group at higher risk of cot death, can account for at the most 5% of the impressive rise. Another well known risk factor, maternal smoking, decreased rather than increased during this period.

The incidence of SIDS has also risen in Sweden,^{61 62} as well as in other Scandinavian countries.^{63 64} These countries are similar to The Netherlands in that they all had low infant mortality and all had a low incidence of cot death. Analysis of the trend in SIDS in Scandinavia is, however, more reliable because of the higher necropsy rates. The Swedish incidence increased from 0.48/1000 live births in 1976⁶¹ to 0.94 in 1984-6.⁶² The traditional sleeping position has also changed in Sweden since 1976, from supine to prone, although there is also reason to be unsure whether or not the trends are related.⁶⁵ We have no information about changes in sleeping position in the other Scandinavian countries.

Recently a paper by Beal attracted considerable attention in South Australia.³⁴ Preliminary results showed that both the prevalence of the prone sleeping position and the incidence of cot death has decreased there.⁶⁶ In The Netherlands there was also considerable attention in the press in late 1987 after a lecture held by one of us on the association between cot death and sleeping prone. To gain insight into how care givers react to such adverse publicity two studies were conducted: one among parents of infants born before the publicity and one among parents of infants born in 1988.^{67 68} The publicity seems to have had a great influence on the way parents place their infants for sleep. In the first study 46% of the 659 infants studied always slept prone, and 10% sometimes slept prone before the publicity. Although parents attempted to 'wean' these children from sleeping prone they were not often successful. In the second study of 1763 children born after the publicity only 19% always slept prone and 8% sometimes slept prone. This change in the sleeping position policies of Dutch parents has been well documented. The first Dutch mortality figures indicate a 40% decrease in cot death in 1988 compared with 1987.⁶⁹ This would support the hypothesis that sleeping prone can contribute to the occurrence of cot death.

The data in the histogram are reported by kind permission of the Central Bureau of Statistics, Voorburg, The Netherlands.

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LETTERS TO THE EDITOR

Management of asthma: a consensus statement

SIR,—I wish to comment on the management of asthma in the first year of life reported in the recent consensus statement.¹ It is unfortunate that such reports do not supply references for their contentions nor do they indicate where serious differences of opinion exist.

In particular I would challenge the statement that the more troublesome children under 1 year should be given oral β_2 -stimulants and/or oral xanthines. As far as I am aware there is no evidence that these drugs are of benefit in children under 1 year and two authors of the report have assessed this. In view of the known side effects of these drugs, it seems ill advised to recommend them when they are of no proven benefit and the balance of the literature suggests they may be harmful.

While some studies have found a benefit from nebulised ipratropium bromide in infancy others have not. Similarly there are studies which cannot find any response to corticosteroids.

There is in fact a quite sustainable argument that no drug treatment should be offered to the wheezing infant and that we should concentrate on the prevention or treatment of dehydration and giving oxygen when anoxia occurs.

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1 Warner JO, Götz M, Landau LI, *et al.* Management of asthma: a consensus statement. *Arch Dis Child* 1989;64:1065-79.

Dr Warner comments:

Dr Lines has managed to pick out the two points which did cause considerable concern to the participants at the round table meeting that formulated the consensus statement.

Serious consideration was given to the inclusion of references in the document, but this would have affected its readability. Furthermore in order to provide a fair and complete documentation, it would have been necessary to include some 200-300 references. This clearly would not have been practical and for the more contentious areas, it would have been necessary to quote virtually every reference relating to the issues.

As outlined in the last section of the document, it was clear that treatment of asthma in children less than 1 year of age was being

recommended mainly on clinical anecdote rather than from firm scientific evidence. There are exceedingly few controlled trials of any form of treatment in this age group. As Dr Lines rightly points out the value of nebulised ipratropium bromide has become somewhat contentious. There are studies that would suggest that corticosteroids have no value and the one study of nebulised sodium cromoglycate equally would suggest that it was not efficacious. Nevertheless, the clinicians at the consensus were of the opinion that there were situations in which all of these drugs were sometimes of value. It would be a brave paediatrician who denied any treatment to an infantile asthmatic who was in severe difficulties and merely relied on correction of hydration and giving oxygen. We have recently completed a controlled trial of the use of nebulised budesonide in severe infantile asthma. Several of the patients were below 1 year of age, and there is no doubt that this particular compound is of benefit. Hopefully other trials will be conducted with alternative therapeutic modalities, which might allow us to present a more authoritative view on the management of the infant wheezer.

SIR,—The consensus statement on the management of younger children with asthma suggests that, as most dry powder inhalers require a relatively high inspiratory flow rate, a metered dose inhaler with large volume spacer is preferable because of the lower inspiratory flow rate required.¹ The Bricanyl Turbohaler (Astra Pharmaceuticals) is a new type of powder inhaler containing 200 doses of terbutaline sulphate without the carrier powders used in most other dry powder devices. A low inspiratory flow rate of about 25 l/min, the order needed to operate the Nebuhaler valve successfully, is sufficient to operate the Turbohaler.^{2 3}

We studied the ability of 24 children aged 3 to 7 years to use the Bricanyl Turbohaler. Sixteen were aged 3 to 5, and 17 were boys; all had suffered from asthma for one to six years and were stable at the time of the study. Twenty one had not taken a β_2 -agonist in the five hours before the study. Peak expiratory flow rate (PEFR) was measured before and 15 minutes after inhaling 0.5 mg terbutaline from a Bricanyl Turbohaler. The device was inspected to determine the amount of drug cleared. Twenty three children inhaled over 90% of the dose from the Turbohaler at the first attempt. The other child needed one more inhalation to clear the full dose from the device. Twenty children had reliable PEFR recordings before and after inhalation; the mean increase from baseline was 20 l/min (10% improvement; $p < 0.01$). There was no difference in the response between the 12 patients aged 3 to 5 (18 l/min) and those aged over 5 (22 l/min). One child reported tremor after one hour.

This is consistent with an earlier Swedish report that Bricanyl given by the Turbohaler is at least as effective as Bricanyl given by the Nebuhaler in preschool children.⁴ This report showed that young asthmatic children, who can have low inspiratory flow rates, use the Bricanyl Turbohaler successfully and with an

improvement in lung function that is not dependent on their age.

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- 1 Warner JO, Götz M, Landau LI, *et al.* Management of asthma: a consensus statement. *Arch Dis Child* 1989;64:1065-79.
- 2 Gleeson JDA, Price JF. Nebuhaler technique. *Br J Dis Chest* 1988;82:172-4.
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Life threatening illness and hospice care

SIR,—In the article on respite care at Helen House, the authors, by implication, criticise hospital care.¹ 'The ward staff could focus their care . . . on the entire family particularly the siblings', and enabling families to meet similarly affected families, 'may not always be possible on the ward'. Before making these critical comments it would have been easy to have found out that these aspects of care are regularly provided on the wards of the local hospital. For example, recently two older siblings and their mother spent all of the Christmas holiday in the ward with their dying sister. Siblings regularly attend outings with their parents and the patient, and there are of course, very active parent support groups that new parents are encouraged to join. We note that many parents experienced 'difficulties in obtaining childminders . . .'. Our nursing staff sometimes babysit for our families in their free time, for no financial gain, and our social workers regularly arrange baby minding and respite care. Finally we recognise the financial problems these families have, and far from being 'beyond the remit' of our service, we pay for the mortgage, travel, holidays, and outings, etc, as needed.

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1 Stein A, Forrest GC, Woolley H, Baum JD. Life threatening illness and hospice care. *Arch Dis Child* 1989;64:697-702.

Drs Stein, Forrest, Woolley, and Baum comment:

The Helen House studies seek to define the role of this children's hospice in providing respite care for children with life threatening illness and their families. It is not our intention to criticise hospital care, let alone that provided by the premier staff at the John Radcliffe Hospital. We would hope that our colleagues would welcome this attempt to illuminate the many dimensions and unmet needs of chronic life limiting disease in childhood by this direct study of the families involved. In this way we may assist with the rational development of a suitable network of care across the country provided by both hospital and hospice staff, linked closely with community based and family orientated social, health visiting, and primary care services.

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Volume 149 No. 3 1989

The pioneers of pediatric medicine
151

Review

Benign partial epilepsy and related conditions: multifactorial pathogenesis with hereditary impairment of brain maturation
H. Doose, W. K. Baier 152

Endocrinology

Wilms tumour in a patient with growth hormone replacement therapy
T. Momoi, C. Yamanaka, T. Yorifuji, H. Sasaki, M. Kaji, Y. Akiyama, Y. Inomata, K. Tanaka, H. Mikawa 159

Hematology/Oncology

Osteonecrosis of vertebrae in a child with acute lymphocytic leukaemia during L-asparaginase therapy
T. Hanada, Y. Horigome, M. Inudoh, H. Takita 162

Immunology/Allergy

Serum IgG subclass concentrations in healthy subjects at different age: age normal percentile charts
A. Plebani, A. G. Ugazio, M. A. Avanzini, P. Massimi, L. Zonta, V. Monafò, G. R. Burgo 164

IgG₂/IgG₄ subclass deficiency in a patient with chronic mucocutaneous candidiasis and bronchiectases
C. Brägger, R. A. Seger, R. Aeppli, F. Hallé, W. H. Hitzig 168

Possible association of sudden infant death with partial complement C4 deficiency revealed by post-mortem DNA typing of HLA class II and III genes

P. M. Schneider, C. Wendler, T. Riepert, L. Braun, U. Schacker, M. Horn, H. Althoff, R. Mattern, C. Rittner 170

Development of hypogammaglobulinaemia in a patient with common variable immunodeficiency
A. Ishizaka, M. Nakanishi, S. Yamada, Y. Sakiyama, S. Matsumoto 175

Fatal infectious mononucleosis with staphylococcal pyoderma in a girl with hereditary immunological dysregulations
T. Inaba, R. Hanada, A. Yaginuma, Y. Hayashi, K. Yamamoto, H. Hukada 177

Facial dysmorphism, parathyroid and thymic dysfunction in the father of a newborn with the DiGeorge complex
P. D. Maaswinkel-Mooij, S. E. Papapoulos, E. J. A. Gerritsen, A. H. Mudde, J. J. P. Van De Kamp 179

Medical genetics

Osteogenesis imperfecta in childhood: cardiac and renal manifestations
U. Vetter, B. Maierhofer, M. Müller, D. Lang, W. M. Teller, R. Brenner, D. Frohneberg, O. Wörsdörfer 184

Keutel syndrome: a report of four cases
H. E. Khosroshahi, Ö. Uluoğlu, R. Olguntürk, C. Başaklar 188

Metabolic diseases

No reduction of high density lipoprotein₂ during weight reduction in obese children and adolescents
K. Zwiauer, B. Kerbl, K. Widhalm 192

4-Hydroxybutyric aciduria: further clinical heterogeneity in a new case
W. Onkenhout, P. D. Maaswinkel-Mooij, B. J. H. M. Poorthuis 194

Neonatology

The male disadvantage in very low birthweight infants: does it really exist?
S. P. Verloove-Vanhorick, D. M. van Zeben-van der Aa, R. A. Verwey, R. Brand, J. H. Ruys 197

Tracheal agenesis: a case report
T. Statz, J. Lynch, M. Ortmann, B. Roth 203

Nephrology/Urology

Frequent relapser minimal change nephrosis: an unrecognized X-linked disorder?
N. B. Awadalla, A. S. Teebi, A. Y. Elzouki, A. Shaltout 205

Exogenous prostaglandin administration and pseudo-Bartter syndrome
J. P. Langhendries, V. Thiry, E. Bodart, G. Delfosse, L. Whitofski, O. Battisti, J. M. Bertrand 208

Neuropediatrics

Symptomatology in children with focal sharp waves of genetic origin
H. Doose 210

Role of protein C in childhood cerebrovascular occlusive accidents
S. Uysal, B. Anlar, C. Altay, S. Kirazli 216

Pharmacology

Blood concentrations after accidental cyclosporin overdose
K. de Meer, R. H. J. Houwen, C. M. A. Bijleveld, D. R. A. Uges, M. J. H. Slooff 219

Preventive pediatrics and epidemiology

Sauna habits and related symptoms in Finnish children
L. Markkola, K. J. Mattila, M. J. Koivikko 221

Indexed in *Current Contents*



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